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RATE OF EVACUATION OF VARIOUS FOODS FROM THE NORMAL STOMACH

A PRELIMINARY COMMUNICATION *

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Since the time of Beaumont it has been known that proteins pass out of the stomach more rapidly than fats, and that carbohydrates are evacuated still more quickly. As the hypotheses advanced in explanation of these differences appeared to be inadequate, it seemed to us advisable to do some further work on this subject, especially with reference to the question why fats are held in the stomach so much longer than carbohydrates. During the course of the investigation, the differences in behavior of substances having little or no food value excited and retained our interest.

Beaumont's observations on the time of evacuation of carbohydrates, proteins and fats, have been confirmed by many workers employing various methods. Penzoldt [1] passed stomach tubes in a number of men. Pavlov [2] and his pupils used dogs with duodenal and other kinds of fistulas. Cannon [3] made roentgen observations on cats, estimating the degree of gastric emptying from the length of the shadows in the intestine. Fermi [4] killed dogs at definite intervals after meals, and weighed the dried gastric residues. McClure, Reynolds and Schwartz [5] mixed barium sulphate with food, and observed the passage fluoroscopically in man. They found that all substances commence to leave the stomach as soon as ingested, but that the total evacuation of some materials was much slower than that of others. Hawk, Rehfuss and Bergeim [6] passed small tubes into the stomachs of human subjects, and

* Submitted for publication, May, 1929.

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1. Penzoldt, F.: Deutsches Arch. f. klin. Med. **51**:535, 1893.
2. Pavlov, I. P.: The Work of the Digestive Glands, ed. 2, London, 1910.
3. Cannon, W. B.: Am. J. Physiol. **20**:283, 1907.
4. Fermi, C.: Arch. f. Physiol., 1901, supp., p. 1.
5. McClure, C. W.; Reynolds, L., and Schwartz, C. O.: On Behavior of Pyloric Sphincter in Normal Man, Arch. Int. Med. **26**:410 (Oct.) 1920.
6. Hawk, P. B.; Rehfuss, M. E., and Bergeim, O.: Am. J. M. Sc. **171**:359, 1926.

removed small portions of the meals at intervals. They found the average evacuation time for 100 Gm. of beef to be three hours; puddings, two and one quarter hours; bacon, four and one half hours, etc.

Pavlov, and later Cannon, explained the differences in the rate of evacuation by the hypothesis of the acid control of the pylorus. This hypothesis was, in brief, that any acid in the antrum opened the pyloric sphincter, whereas the presence of any acid in the duodenum resulted in closure of the pylorus until such time as the duodenal contents had been neutralized. On leaving the stomach, carbohydrates are neutral and proteins are distinctly acid, whereas fats are broken up into fatty acids and glycerol on arrival in the duodenum. This hypothesis, therefore, fitted in with the known facts and seemed to explain satisfactorily the differences observed.

Support of the acid control hypothesis was found in the work of Lintwarew,[7] who placed fat in the duodenum and observed that gastric evacuation was thereby markedly slowed. It is of interest to note that Edelman[8] failed to find the same effect with petrolatum. Marbaix[9] found that the emptying of the stomach was delayed when he placed milk or egg yolk in the jejunum. Tonnis and Never[10] recently showed that any free acid, fatty or otherwise, when injected into the duodenum caused closure of the pylorus, whereas neutralized fatty acids had no such effect. Procaine hydrochloride abolished the reflex closure.

The following observations, however, raised doubts as to the truth of the acid control hypothesis. McClure, Reynolds and Schwartz[5] observed that neutralizing the duodenal contents had little effect on the rate of gastric evacuation, and further showed that the pylorus opened and chyme entered the duodenum "on the approach of each antral peristaltic wave." In Cannon's[11] own experiments the chyme left the stomach as peristaltic waves approached the pylorus, though not with every wave. Baird, Campbell and Hern[12] found that acid in the duodenum did not close the pylorus. Sick and Tedesco[13] placed acids and alkalis in the duodenum and observed no change in gastric or pyloric activity. Carlson and Litt,[14] employing an improved balloon method, found that any substance, acid, alkaline, or neutral, when placed

7. Lintwarew, S. J.: Biochem. Central **1**:96, 1903.

8. Edelman, J. A., quoted by Babkin, B. P.: Die aussere Sekretion der Verdauungsdrusen, ed. 2, Berlin, 1928, p. 824.

9. Marbaix, O.: Cellule **14**:251, 1898.

10. Tonnis, W., and Never, H. E.: Arch. f. d. ges. Physiol. **207**:24, 1925.

11. Cannon, W. B.: Am. J. Physiol. **1**:359, 1898.

12. Baird, M. M.; Campbell, J. M. H., and Hern, J. R. B.: Guy's Hosp. Rep. **74**:23, 1924.

13. Sick, K., and Tedesco, F.: Deutsches Arch. f. klin. Med. **92**:416, 1908.

14. Carlson, A. J., and Litt, S.: Visceral Nervous System: Reflex Control of Pylorus, Arch. Int. Med. **33**:281 (March) 1924.

in the duodenum caused closure of the pylorus. Finally, Barsony and Hortobagyi [15] showed that strong acid in the duodenum inhibited gastric emptying, but not because of pyloric closure. The delay was due to depression of the peristaltic waves of the stomach.[16]

As it becomes evident that acid control is not the only factor, or even the principal influence, in determining the rate of the emptying of the stomach, more and more is attention being turned to the mechanical forces involved, and especially to gastric peristalsis. It therefore becomes of interest to consider the factors which are known to influence peristalsis and gastric evacuation, and the following is a partial list of these.

The physical state of the foodstuff is of considerable importance, as gruel leaves the stomach more rapidly than dry carbohydrates (Hedblom and Cannon [17]), and large lumps of meat are retained much longer than minced meat (London [18]). Posture and exercise have marked effects (Neilson and Lipsitz,[19] Dickson and Wilson [20]); changes in the carbon dioxide content of the blood have a great influence (Dickson and Wilson), also the rate of utilization of glycogen (Bulatao and Carlson [21]), emotions (Cannon,[11] Bennett and Venables,[22] Hughson [23]), fractures of bones (Alvarez [24]), colonic irritation (Hedblom and Cannon,[16] White [25]), smoking, drinking water with meals (Ivy [26]) and many drugs such as strychnine, atropine, caffeine and alcohol. It is highly probable that other influences will be found to affect both peristalsis and the rate of emptying, and it is possible that the increased fat in the blood after a fat meal (Neisser and Braeuning,[27] Bloor [28]) may be one of these.

15. Barsony, T., and Hortobagyi, B.: Arch. f. d. ges. Physiol. **210**:300, 1925.

16. For a more extensive review of the work on this subject, see Alvarez: The Mechanics of the Digestive Tract, ed. 2, 1928, p. 175; also Babkin: Die aussere Sekretion der Verdauungsdrüsen, ed. 2, 1928, p. 802.

17. Hedblom, C. A., and Cannon, W. B.: Am. J. M. Sc. **138**:504, 1909.

18. London, E. S.: Experimentelle Physiologie und Pathologie der Verdauung, Berlin, Urban & Schwarzenberg, 1925, p. 52.

19. Neilson, C. H., and Lipsitz, S. T.: The Effect of Various Procedures on the Passage of Liquids from the Stomach, J. A. M. A. **64**:1052 (March 27) 1915.

20. Dickson, W. H., and Wilson, M. J.: J. Pharmacol. & Exper. Therap. **24**: 33, 1924.

21. Bulatao, E., and Carlson, A. J.: Am. J. Physiol. **69**:107, 1924.

22. Bennett, T. I., and Venables, J. F.: Brit. M. J. **2**:662, 1920.

23. Hughson, W.: Reflex Spasm of Pylorus and Its Relation to Diseases of Digestive Organs, Arch. Surg. **11**:136 (July) 1925.

24. Alvarez, W. C.: The Mechanics of the Digestive Tract, ed. 2, 1928, p. 197.

25. White, F. W.: Am. J. M. Sc. **156**:184, 1918.

26. Ivy, A. C.: Am. J. Physiol. **46**:420, 1918.

27. Neisser, E., and Braeuning, H.: Ztschr. f. exper. Path. u. Therap. **4**:747, 1907.

28. Bloor, W. T.: J. Biol. Chem. **23**:317, 1915.

METHOD

In this investigation, roentgen observation of the human subject was adopted as the method which best met our requirements. All the experiments were performed on four young men who had no symptoms of gastro-intestinal or other disease, and whose stomachs had previously been found to be normal on fluoroscopic examination. All had fasted for at least four hours preceding the experiments. The subject was given a meal containing 40 Gm. of barium sulphate made up to 240 cc., with the substance to be investigated. Fluoroscopic observations were made during the consumption of the meal, with the object of determining how soon the food commenced to leave the stomach. Subsequent observations were made at one and one-half, three and four and one-half hours after beginning the ingestion of the meal, and at each examination an estimate was made of the percentage of the barium remaining in the stomach. The results are expressed as the percentage of the meal which had been evacuated from the stomach.

In some instances the meals employed were patterned on those described by McClure, Reynolds and Schwartz.[5]

Standardization has been achieved in the amount of barium, the volume and temperature of the meal, the time of the day and the day of the week on which it was consumed, and the amount of exercise of the subject. If the subject had a "cold in the head," or otherwise did not feel well, the experiment was deferred. Nearly all the observations of the percentages in the stomach were made by one of us (A. C. S.), and all were checked by one of the others. We are therefore confident that any errors due to method have been reduced to a minimum. It is probable that no change has occurred in the motility of subject D's stomach during the four years that this investigation has been in progress, for a meal of thick oatmeal porridge consumed March 21, 1929, behaved in every respect almost exactly like a similar meal taken March 4, 1925.

The observations with respect to meals consumed by two or more subjects are summarized in table 1. A further series of experiments was performed on subject D, and all the observations on this person are shown in table 2.

COMMENT

Any discussion of gastric emptying must of necessity bring up the question of the physical forces which are concerned in that emptying. Among these forces are gravity, the contraction of the stomach as a whole and gastric peristalsis. It is not our intention to discuss this question in this paper. It can be stated, however, that with one exception, in the experiments here recorded, no barium was ever seen to enter the duodenum except on the approach of a gastric peristaltic wave. The single exception was in the case of the meal containing 30 Gm. of Witte's peptone. The first mouthful passed through the stomach, pylorus, duodenum and upper part of the jejunum in the course of a few seconds; then the shadow was halted in the region of the pyloric sphincter, and no further emptying occurred until five minutes later, when peristalsis had become established.

TABLE 1.—*Observations on Four Subjects with Six Different Meals**

Subject	Thick Porridge 240 Cc.				100 Gm. Dates and Bread 40 Gm.				140 Gm. Ground Lean Meat				120 Gm. Fat Bacon 5 Egg Yolks				240 Cc. 32 per Cent Cream				240 Cc. 32 per Cent Cream + 0.5 Gm. Hydrochloric Acid			
	Percentage Out in				Percentage Out in				Percentage Out in				Percentage Out in				Percentage Out in				Percentage Out in			
	First Leaving	1½ Hrs.	3 Hrs.	4½ Hrs.	First Leaving	1½ Hrs.	3 Hrs.	4½ Hrs.	First Leaving	1½ Hrs.	3 Hrs.	4½ Hrs.	First Leaving	1½ Hrs.	3 Hrs.	4½ Hrs.	First Leaving	1½ Hrs.	3 Hrs.	4½ Hrs.	First Leaving	1½ Hrs.	3 Hrs.	4½ Hrs.
A	1	85	100	..	..	..	..	..	3	50	75	75	15	20	30	50	2	?	40	50	2	40	50	60
B	2	70	100	..	3	55	95	..	4	50	60	75	31	10	50	85	2	40	50	75	1	30	40	60
C	3	95	..	..	..	..	..	..	12	70	100	..	..	..	..	..	2	50	65	75	..	..	..	..
D	4	75	90	..	3	60	95	..	7	40	80	90	12	10	30	95	1	75	80	85	1	710	75	90

* With each meal the first column shows the time in minutes after the commencement of ingestion that barium was first seen in the duodenum. The other three columns give the percentage of the meal which has left the stomach in one and one-half, three and four and one-half hours, respectively. Each meal totals 240 cc. and contains 40 Gm. of barium sulphate.

For our present purpose, therefore, we shall assume that gastric peristalsis is the principal force concerned in normal gastric evacuation.

The rôle of the pyloric sphincter in influencing normal gastric emptying is another question that we shall not discuss here. In all our

TABLE 2.—*Observations on Subject D* *

Meal	Minutes to Swallow	First Leaving	Percentage Out in 1½ Hrs.	3 Hrs.	4½ Hrs.	Comment
Thick porridge	3	4	75	90	..	
Thick porridge	2	4	75	95	..	
Thick porridge/400 cc. 32 per cent cream	3	5	65	85	100	7½ hours after
Thick porridge, plus 1.3 cc. hydrochloric acid (38%)	2	6	75	80	85	
Very thick porridge, plus 1.3 cc. hydrochloric acid (38%)	3	5	60	90	100	
Thick porridge, 200 Gm.; washed bran, 24 Gm.	4	22	10	75	85	
Bread, 40 Gm.; dates, 100 Gm.	4	38	35	60	70	
Meat, 140 Gm., ground, lean, baked	3	3	60	95	..	
Codfish, boiled, 160 Gm.	5	7	40	80	90	
Egg white, raw, 225 Gm.	5	20	30	85	95	Contains no carbohydrates
Egg white, raw, 220 Gm.	1	5	30	65	85	
Egg white, cooked, 190 Gm.	1	3	75	85	90	Put through sieve
Gelatin, 15 Gm.; white of egg (1)	5	41	65	95	..	
Witte's peptone, 30 Gm. in water	2	5	60	90	..	
Witte's peptone, 70 Gm. in water	1	½	90	95	..	
Asparagin, 35 Gm., in water	1	10	30	60	85	Very viscid
Cream 32%	1	1	75	100	..	
Cream, 32%	1	1	75 ?	80	85	Severe cramps
Cream plus tube	1	1	25	40	70	Severe cramps
Cream plus tube	1	1	10 ?	60	95	Tube in duodenum continuous suction
Cream plus tube	1	1	25	75	100	Tube in duodenum, no suction
Cream plus 0.5 Gm. hydrochloric acid	1	1	10 ?	75	85	Free acid, 0; total acid, 40
Cream plus 5 Gm. $NaHCO_3$	1	1	25	40	80	
Bacon, 120 Gm., plus 5 egg yolks	5	12	10	30	95	
Olive oil	1	1	25	50	60	Severe cramps
Liquid paraffin	1	2	80	100	..	No discomfort
Liquid paraffin, 195 cc.; 32% cream, 45 cc.	1	½	75	100	..	
Liquid paraffin, 150 cc.; salt-free butter, 90 Gm.	1	½	60	80	90	Contains approx. same amount of butter fat as 32% cream
Bran, washed, 37 Gm., wet	12	90+	0	20	35	Contains 3 per cent carbohydrate
Bran, washed, 30 Gm., wet	25	51	20	35	50	
Bran, washed, 25 Gm., wet	7	80	2	25	40	More finely divided than above
Bran, unwashed, 38 Gm., wet	12	32+	20	35	50	Contains 50 per cent carbohydrate
Agar, 15 Gm. in water	5	19	40	65	85	
Cabbage, ground, thrice boiled	2	25	25	60	70	200 Gm. wet weight contains no carbohydrate
Spinach, ground, thrice boiled	3	28	60	90	100	240 Gm. wet weight contains no carbohydrate

* The first column gives the time in minutes taken to swallow the meal. The second column shows the time after the commencement of ingestion that barium was first seen in the duodenum. The other three columns give the percentage of the meal which has left the stomach in one and one-half, three and four and one-half hours, respectively. Each meal totals 240 cc. and contains 40 Gm. of barium sulphate.

observations, however, except in the experiments with bran, every peristaltic wave of any considerable depth effected an expulsion of barium into the duodenum, provided that barium was in contact with the sphincter. Shallow waves at the commencement of the meal may

not cause emptying for one or two minutes, and toward the end of an experiment the remaining barium may be seen in a narrow band along the most dependent part of the greater curvature when the subject is standing, and hence may not be evacuated even by deep peristaltic waves. Our impression is that the pyloric sphincter behaves as a part of the gastric musculature, being strongly contracted only on the arrival of a peristaltic wave, and that normally it has no independent influence on evacuation in the stomach.

The question of the effect of acid on gastric evacuation is too involved for adequate discussion here. The following points, however, seem worthy of note. For many years we have observed that, in patients with organic lesions or functional disturbances, meals consisting of buttermilk and barium sulphate have been associated with shallow peristalsis, pylorospasm, and retarded gastric evacuation, as compared with watery suspensions, or meals of barium and whole milk. The pylorospasm is usually temporary, seldom persisting for more than from five to ten minutes.

In two experiments on subject D, porridge meals were made strongly acid with hydrochloric acid. The results were inconclusive; after one meal shallow peristalsis and retarded evacuation were observed, while observations following the other were normal.

Filling of the Stomach.—In order to understand the passage of a meal through the pyloric sphincter, it will be necessary to consider the manner in which the meal traverses the stomach in order to reach the sphincter. Meals of different consistency behave differently in this respect. A liquid meal such as cream, weak peptone solution or liquid paraffin at once forms a narrow streak along the whole length of the stomach from the cardia to the pyloric sphincter. As swallowing continues, the stomach widens. A meal of this type was commenced at 4.30 and finished at 4.30: 40 (fig. 1).

A more solid meal, however, at first forms a ball at the cardiac end of the stomach, and then this mass becomes pointed and slowly descends to the region of the pylorus. The meal of spinach for example behaved as shown in figure 2.

This meal was commenced at 3.30 and finished at 3.36 (compare Groedel [29]).

The Initiation of Peristalsis.—Peristalsis of the stomach was visible, in the case of nearly all liquid meals, within one minute of the commencement of ingestion, and continued to be visible until only a small quantity of barium remained in the stomach. On the other hand, after a more solid meal, such as ground lean meat, codfish or cabbage, no peristaltic waves could be seen until the "head" of the meal had reached

29. Groedel, F. M.: Die Magenbewegungen, Hamburg, 1912.

the pyloric sphincter. Thus peristalsis commenced much earlier with liquid meals than with solid ones. The nature of the initial stimulus to peristalsis is a matter of considerable interest, but at present we can only speculate on this problem. It cannot be due to the presence of material in any part of the stomach, for in one experiment in which bran was used the meal filled the whole of the stomach, including the pyloric part, for at least forty-five minutes without a trace of peristalsis, and Rogers and Martin [30] have shown that peristaltic waves can occur when the stomach contains nothing but the normal gas bubble. It cannot be due to absorption from the stomach, for peristalsis commenced immediately after the ingestion of barium and liquid paraffin, which are not absorbed.

The Depth of Peristaltic Waves.—With all fluids the waves were shallow for a minute or so, and then became deeper; later they became

Fig. 1.—Appearance of stomach at 4.30:20, 4.30:40, and 4.31, respectively, following the ingestion of a liquid meal.

Fig. 2.—Appearance of stomach at 3.36, 3.41, 3.46, 3.51 and 4.01, respectively, following the ingestion of a more solid meal.

shallow again in the case of cream, olive oil and a mixture of liquid paraffin and butter, but remained deep with liquid paraffin alone, with weak peptone solution, and with asparagin (an amino-acid) and water. Thus the waves became shallow with fat meals, but remained deep in the case of meals which contained no fat. The interpretation of these observations will be considered a little later.

The Initial Emptying of the Stomach.—The initial emptying depends, in the first instance, on the presence of meal material in the region of the pyloric sphincter, and this, as already shown, varies with the consistency of the meal. Thus the first evacuation is rapid for all liquids and slow for all solids. Within one or two minutes of the "head" of the liquid meal reaching the pyloric sphincter, some barium was seen

30. Rogers, F. T., and Martin, C. L.: Am. J. Physiol. **76**:349, 1926.

to enter the duodenum. The same was true for solid meals, with a few exceptions, the most important of which were meals containing bran. In one experiment in which bran was used the stomach was quiescent, without peristalsis, and with barium apparently in contact with the pyloric sphincter, for at least forty-five minutes. As soon as peristalsis became established, some of the bran entered the duodenum. Thus the presence of adequate peristalsis is a second requirement for normal gastric evacuation.

The influence of the consistency of the meal was shown in another experiment with bran. In this observation, peristalsis commenced as soon as the "head" of the meal reached the pyloric sphincter; following this, at intervals for over an hour we watched the peristaltic waves sweeping over the stomach, without the least fleck of barium entering the duodenum. Our impression during the observation was that emptying was hindered by friction of the bran with the mucous membrane of the stomach, rather than by obstruction from a closed pyloric sphincter. Subsequently barium left the stomach regularly, although at a slow rate. It seems not unlikely that friction was eventually overcome by a secretion of mucus sufficient to coat the rough edges of the bran.

The initial emptying of the stomach therefore appears to depend on two factors: the consistency of the meal and the presence of peristalsis of adequate depth.

Further Progress of Evacuation.—A study of the tables will show that, after the initial emptying, the various meals left the stomach at widely different rates. These differences can, we think, be satisfactorily explained by the two factors,—the consistency of the meal, and the depth of the peristaltic waves.

The influence of the consistency of the meal is best illustrated by the behavior of the substances of little or no food value. Thus liquid paraffin left the stomach much more rapidly than bran, while agar occupied an intermediary position. As far as we know, these substances excite little gastric secretion, and hence their consistencies probably do not change appreciably in the stomach.

Many foodstuffs, such as meats and vegetables, excite a secretion of gastric juice. The consistency, and therefore the rate of evacuation, of a meal may thus undergo alteration in the stomach, not only from the presence of the gastric juice, but also from its digestive action.

The depth of the peristaltic waves was found to be shallow in the case of meals which contained fat. Two explanations of this difference present themselves; the fatty acids of fat digestion may irritate the duodenum and affect peristalsis through nerve impulses, as suggested by Barsony and Hortobagyi,[15] or some product of fat digestion circulating in the blood may depress muscular activity and influence the depth of the waves. The latter explanation appears to receive support from

observations on hunger contractions of the stomach. Thus Farrell and Ivy [31] found that fat put into a dog's stomach inhibited the contractions of a stomach pouch which had been completely separated from the stomach and implanted in a new position just under the skin.

In two experiments a large meal of cream was taken seven and one half hours before a meal of thick porridge and barium, the idea being that intestinal absorption of fat would be in full course (Leathes and Raper [32]), although the stomach was empty. The progress of these meals of porridge was definitely slower than that of similar meals taken without the previous ingestion of cream. These observations appear to support the hypothesis that peristalsis of the stomach may be depressed by products of fat digestion circulating in the blood. We cannot, however, rule out the possibility that impulses from the jejunum or ileum were operating to depress peristaltic activity.

SUMMARY

1. The initial emptying of the stomach depends on two factors;—the presence of peristalsis of adequate depth, and the consistency of the meal.

2. All liquid meals start to leave the stomach as soon as ingested, regardless of their composition. Most solids commence to leave the stomach as soon as they reach the pyloric sphincter.

3. After the first few minutes, proteins are evacuated more slowly than carbohydrates, and fats are slowest of all.

4. In the case of fats this delay is associated with shallower peristaltic waves, due possibly to depression of muscular activity by products of fat digestion circulating in the blood.

31. Farrell, J. I., and Ivy, A. C.: Am. J. Physiol. **76**:227, 1926.
32. Leathes, J. B., and Raper, H. S.: The Fats, London, 1925, p. 134.

BLOOD PRESSURE IN DIABETES MELLITUS

A STATISTICAL STUDY *

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The subject of blood pressure in diabetes mellitus has aroused considerable controversy during recent years, and yet there is no unanimity of opinion on the matter at the present time. With the discrepancies in the literature in mind, a statistical study of the problem has been undertaken. Obviously, in order to make such a study, some standard must be used for comparison. In the analysis of the data presented in this paper the blood pressures of the diabetic persons are compared with those of three control series: (1) a group of dispensary patients; (2) a group of hospital patients, and (3) a so-called normal group. A necropsy series of diabetic cases is also studied.

LITERATURE

In 1733, Stephen Hales [1] performed his memorable experiment on the blood pressure of the horse, in which, after the insertion of a brass pipe into the crural artery, the "blood rose in the tube eight feet three inches perpendicular above the level of the left ventricle of the heart." In 1828, Poisseulle [2] introduced the mercury manometer as a means of recording blood pressure, and in 1847, Ludwig combined the mercury and the graphic methods, so that permanent records of the blood pressure were available.

Little was done on the blood pressure of man, however, until 1896, when Riva-Rocci [3] devised the armlet method for taking pressures, and the knowledge of human blood pressure dates from that time. In the subsequent year, Hill and Bernard [4] devised a similar method. In this early work the width of the armlet of the blood pressure apparatus was variable, although it is now known that the blood pressure varies with armlets of different widths. In 1901, however, von Recklinghausen [5] standardized the width of the cuff. Thus, the knowledge of

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* Abstract of Master's Thesis, Department of Pathology, University of Minnesota, E. T. Bell, M.D., Advisor.

1. Hales, Stephen: Statistical Essays Containing Hemostatics, London, 1733.
2. Poisseulle, quoted by Tigerstedt: Lehrbuch Physiologie des Kreislaufes, Leipzig, S. Hirzel, 1893, p. 322.
3. Riva-Rocci, S.: Gazz. med. di Torino **47**:981, 1896.
4. Hill, L., and Bernard, H.: Brit. M. J. **2**:904, 1897.
5. Von Recklinghausen, H.: Arch. f. exper. Path. u. Pharmakol. **46**:78, 1901.

blood pressure in man really dates from the beginning of the present century, although Vierordt, Marey, Basch and Allbutt, abroad, and Erlanger, Cook, Janeway and many others, in this country, had been working on the problem.

The question arises as to which sounds one should take as representing the points at which the systolic and the diastolic readings should be made. I am cognizant of the fact that there is sometimes an auscultatory gap (trau ausculatoire of the French), in which the first sound appears, disappears and latter reappears as the pressure in the cuff is diminished. This silent phase is most prone to be present in cases of hypertension, and the upper limit of sound is apt to be unobserved unless the pressure in the cuff is elevated to approximately 200 mm. of mercury. Tixier [6] first described this phenomenon in 1918, and in the following year Tixier and Gallavardin [7] observed the silent gap in a case of aortic stenosis. Gibson [8] described the five zones which are observed in taking blood pressures as follows: The first zone is of short duration and is sometimes difficult to detect, since the sounds are soft and dull; in the second zone, which extends over a range of from 20 to 60 mm. of mercury, the quality of the sounds is variable, and it is in this phase that the silent gap occurs when present. The third zone is the most distinctive phase, and here the sounds are loud and snapping and increase in intensity to a maximum, when they suddenly change to the fourth zone; this zone is of short duration, and here the sounds are soft and dull. In the fifth zone, the sounds disappear. The point at which the first sound is heard in the first zone represents the systolic pressure, and the sudden change in the character of the sounds in the fourth zone marks the point at which the diastolic pressure should be taken.

The pressures obtained by the oscillation method are higher than those determined by either the palpation or the auscultation method, and are less accurate than the readings obtained by the use of the combined methods. Consequently, the combined method has been used in obtaining the data for the present paper.

What should be considered as the normal blood pressure? A voluminous literature has accumulated on this subject. I am chiefly concerned with the blood pressure in the older age groups, but Burlage,[9] Melvin and Murray,[10] Addis [11] and Conception and Bulatao [12] found

6. Tixier, L.: Paris méd. **27**:502, 1918.
7. Tixier, L., and Gallavardin, L.: Arch. d. mal. du coeur **12**:447, 1919.
8. Gibson, P. C.: Lancet **2**:1012, 1927.
9. Burlage, S. R.: Proc. Soc. Exper. Biol. & Med. **19**:247, 1922.
10. Melvin, G. S., and Murray, J. R.: J. Exper. Physiol. **15**:125, 1914-1915.
11. Addis, T.: Blood Pressure and Pulse Rate Reactions, Arch. Int. Med. **30**: 240 (Aug.) 1922.
12. Conception and Bulatao: Philippine J. Sc. **2**:135, 1916.

that for the first three decades of life the average systolic blood pressures are well below 130 mm. of mercury.

As one advances to the older age groups, it is found that there is considerable controversy over the mean systolic blood pressures. Wiggers [13] stated that a value of from 100 to 125 mm. of mercury by the palpation method may be taken as the normal systolic blood pressure before middle life, and that a value of perhaps 10 mm. higher may be expected after that period.

Richter [14] found the average systolic pressure for persons between the ages of 62 and 89 to be 153 mm. of mercury. Saller [15] found that the systolic pressure in women is higher than that in men in the older age groups, being more than 150 mm. after the age of 56 in women, while the systolic pressure in men of the corresponding age group is 136 mm. Reilingh [16] expressed the belief that the average systolic pressure for persons over the age of 60 is 168 mm. of mercury, and Wildt [17] found that the average pressure for persons of the same age group is 150 mm. Sachs [18] found the average systolic blood pressure in persons of 70 years or more to be 180 mm. of mercury. Janeway,[19] Norris, Bazett and McMillan,[20] Hensen [21] and Goldscheider [22] suggested that 160 mm. of mercury be taken as the upper limit of normal systolic blood pressure in older persons.

On the other hand, I found many articles in the literature in which the systolic blood pressures are much lower than those cited. Symonds,[23] in a study of 150,000 cases, divided into five-year age groups, found the highest systolic value to be 142 mm. of mercury, and this pressure was found in the oldest age group. Woley,[24] in a series of 1,000 persons of all ages, found the average systolic pressure to be 127.5 mm for males and 120 for females. Fisher [25] reported the highest systolic

13. Wiggers, C. J.: Modern Aspects of Circulation in Health and Disease, Philadelphia, Lea & Febiger, 1923, p. 359.

14. Richter, A.: Deutsches Arch. f. klin. Med. **148**:3, 1925.

15. Saller, K.: Ztschr. f. d. ges. exper. Med. **58**:683, 1928.

16. Reilingh, quoted by Sachs, H.: Jahresk. f. ärztl. Fortbild. **18**:20, 1927.

17. Wildt, H.: Zentralbl. f. Herzkrankh. **4**:41, 1912.

18. Sachs, H.: Jahresk. f. ärztl. Fortbild. **18**:20, 1927.

19. Janeway, T. C.: A Clinical Study of Hypertensive Cardiovascular Disease, Arch. Int. Med. **12**:755 (Dec.) 1913.

20. Norris, G. W.; Bazett, H. C., and McMillan, T. M.: Blood Pressure: Its Clinical Applications, Philadelphia, Lea & Febiger, 1927.

21. Hensen: Deutsches Arch. f. klin. Med. **67**:438, 1900.

22. Goldscheider, quoted by Sachs, H.: Jahresk. f. ärztl. Fortbild. **18**:20, 1927.

23. Symonds, B.: Blood Pressure of Healthy Men and Women, J. A. M. A. **80**:232 (Jan. 27) 1923.

24. Woley, A. P.: The Normal Variation of the Systolic Blood-Pressure, J. A. M. A. **55**:121 (July 9) 1910.

25. Fisher, J. W.: The Diagnostic Value of the Sphygmomanometer in Examinations for Life Insurance, J. A. M. A. **63**:1752 (Nov. 14) 1914.

pressure in the 56 to 60 year group, in which the pressure was 135 mm. of mercury. Dunham,[26] in 8,645 apparently normal soldiers, found the highest systolic pressure in the 50 to 64 year group, in which it was 134 mm. of mercury.

That there is a positive correlation between systolic blood pressure and increase in body weight above normal is shown by the work of Dunham,[26] Dublin, Fisk and Kopf,[27] Faber [28] and Symonds.[23]

Before entering into a discussion of the literature on the subject of the blood pressure in diabetes mellitus, I shall mention a few articles which have been published pertaining to the relation between blood pressure and blood sugar levels. Hopkins [29] and Frank [30] found that a moderate hyperglycemia occurs in many cases of hypertension. Neubauer [31] and Botti [32] also noted a relationship existing between hyperglycemia and high blood pressure. O'Hare [33] and Kylin [34] showed the relation between hypertension and low carbohydrate tolerance. Hopkins [29] concluded that four clinical features occur together: hypertension, hyperglycemia, arteriosclerosis and obesity. Harle [35] failed to find any exact parallelism between the blood sugar and the blood pressure curves, although one fourth of his cases showed a moderate hyperglycemia. Peiser,[36] on the other hand, found no elevation of the blood sugar level in cases of hypertension uncomplicated by diabetes mellitus.

The literature is divided in regard to the question of the blood pressure in diabetes mellitus. Vaquez,[37] Orr,[38] Kahn,[39] Janeway [40] and Elliot [41] expressed the belief that the systolic blood pressure is not elevated in uncomplicated cases of diabetes. Rosenbloom [42] also sub-

26. Dunham, G. C.: Internat. Clin. **3**:81, 1925.
27. Dublin, L. I.; Fisk, E. L., and Kopf, E. W.: Am. J. M. Sc. **170**:576, 1925.
28. Faber, A.: Skandin. Arch. f. Physiol. **45**:189, 1924.
29. Hopkins, A. H.: Am. J. M. Sc. **149**:254, 1915.
30. Frank, E.: Deutsches Arch. f. klin. Med. **103**:397, 1911.
31. Neubauer, E.: Ztschr. Biochem. **25**:284, 1910.
32. Botti, A.: Policlinico **29**:249, 1922.
33. O'Hare, J. P.: Am. J. M. Sc. **160**:366, 1920.
34. Kylin, E.: Zentralbl. f. inn. Med. **42**:783, 1921; ibid. **44**:81, 1923.
35. Harle, F.: Ztschr. f. klin. Med. **92**:124, 1921.
36. Peiser, F.: Ztschr. f. klin. Med. **106**:290, 1927.
37. Vaquez, H.: Gaz. d. hôp. **78**:1221, 1904.
38. Orr: Montana M. J. **31**:833, 1902.
39. Kahn, Max: Angina Pectoris of Diabetes, J. A. M. A. **76**:570 (Feb. 26) 1921.
40. Janeway, T. C.: Bull. Johns Hopkins Hosp. **26**:341, 1916.
41. Elliot, A. R.: A Clinical Study of Blood Pressure Variations in Diabetes and Their Bearing on the Cardiac Complications, J. A. M. A. **49**:27 (July 6) 1907.
42. Rosenbloom, J.: J. Lab. & Clin. Med. **7**:392, 1922.

scribed to this view, although in his series a systolic pressure of 150 mm. or more was found in 40 per cent of the cases; of 170 mm. or more in 17 percent and of 200 mm. or more in 12 per cent. Adams [43] and Kahn [59] expressed the opinion that when hypertension is present in persons affected with diabetes mellitus the elevated blood pressure is suggestive of the presence of some other condition, which is of itself producing the hypertension.

On the contrary, many investigators believe that the blood pressure in diabetic persons tends to be elevated. Potain [44] found that the blood pressure in diabetes is even higher than in nephritis. Joslin [45] stated that in patients affected with diabetes mellitus the blood pressure tends to be below normal in those under the age of 35, after which it is slightly above normal. He stated, "The interval between diabetic and normal widens as age advances." Bell and Clawson [46] found that 42.5 per cent of the patients with diabetes in their series had a systolic blood pressure of 150 mm. of mercury or more, and they concluded that hypertension is 2.7 times as frequent in diabetic as in nondiabetic persons over 50 years. Peterson,[47] in a study of the arterioles of the kidney and of the pancreas, found more marked arteriolosclerosis in the diabetic group than in his control series. Kramer,[48] in a study of 500 cases of diabetes mellitus, found a systolic pressure of 150 mm. of mercury or more in 39 per cent. He concluded, "The combination of hyperglycemia and hypertension occurs so frequently that it has ceased to be looked upon as a coincidence." Katz-Klein,[49] in a series of 120 cases of diabetes, found a systolic blood pressure of 160 mm. of mercury or more in 25 per cent. She stated, however, that the blood sugar and the blood pressure curves do not run parallel. Crummer [50] also observed that hypertension is common in cases of diabetes, while Maranon [51] expressed the belief that a high systolic blood pressure may be present prior to the onset of the disease, but tends to fall during its course.

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43. Adams, S. F.: Proc. Staff Meetings Mayo Clinic **3**:303, 1928.

44. Potain, quoted by Allbutt: Diseases of the Arteries, Including Angina Pectoris, New York, The Macmillan Company, 1915, vol. 1.

45. Joslin, E. P.: Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1923.

46. Bell, E. T., and Clawson, B. J.: Primary (Essential) Hypertension, Arch. Path. **5**:939 (June) 1928.

47. Peterson, R. F.: University of Minnesota Thesis, June, 1927.

48. Kramer, D. W.: Am. J. M. Sc. **176**:23, 1928.

49. Katz-Klein, F.: Med. Klin. **20**:1808, 1924.

50. Crummer: M. Herald **21**:46, 1902.

51. Maranon, G.: Zentralbl. f. inn. Med. **43**:169, 1922; Arch. de cardiol. y Hematol. **125**:3, 1922.

STATISTICAL STUDY

In a study of normal blood pressure the consideration of primary importance is to secure normal material. This seems evident, and yet it is surprising to note the number of studies which have been reported in which the blood pressures were assumed to represent normal values, although the subjects on whom the data were accumulated were ill.

In the so-called normal group discussed in this paper the subjects included visitors to the hospital and the personnel of the hospital. Obviously, the greater number of these persons were practically normal.

The instrument used in taking the blood pressures was a Baumanometer with a cuff of standard width. The accuracy of the instrument was checked against two similar instruments before the work was begun, and in all cases care was taken to have the mercury level at zero prior to the elevation of the pressure in the cuff. Although Hill and Rowland [52] found that the blood pressure is practically the same in

TABLE 1.—*Age Distribution in Four Series of Cases*

Age Groups	Normal	Dispensary	Hospital	Diabetic
35-40	57	43	56	18
40-45	50	43	69	30
45-50	55	43	42	44
50-55	54	43	60	82
55-60	54	44	52	84
60-65	61	43	46	89
65-70	57	36	54	31
70-75	61	28	41	22
75 plus	60	33	43	8

the lower and upper extremities normally, care was taken to apply the cuff in approximately the same position in all cases, this being about 2 inches (5 cm.) above the fold of the antecubital space. The pressure in the cuff was elevated to 200 mm. of mercury and gradually lowered, care being taken to observe the auscultatory gap, if present. Prolonged compression by the cuff was avoided, since MacWilliam [53] and others have shown that the continued pressure may modify the readings obtained by the auscultation method. In all cases the palpation and the auscultation methods were combined, as recommended by MacWilliam and Melvin,[54] and the pressure obtained by the former method was constantly less than that obtained by auscultation. The subjects were all observed while in the sitting posture; the readings were taken approximately two hours after meals, and in no case was the blood pressure taken until the subject had been given a rest period. Unfortunately, in the majority of cases only one observation was made. The blood pressures were all taken by me.

52. Hill, L., and Rowland, R. A.: Heart **3**:222, 1912.
53. MacWilliam, J. A.: Physiol Rev. **5**:303, 1925.
54. MacWilliam, J. A., and Melvin, S.: Brit. M. J. **1**:693, 1914.

Three control groups were studied, and the blood pressures in each of these were compared with the pressures in the diabetic series. The first control group consisted of 356 dispensary patients, all of whom were 35 years or older. These were consecutive cases, taken regardless of the conditions for which the patients were being treated. In the second control series the blood pressures in 472 consecutive hospital cases were studied. Again, these cases were taken regardless of the complaint of the patient. In the third control series blood pressures were taken on apparently normal persons, the pressure being taken according to the methods already outlined.

TABLE 2.—*Mean Systolic and Diastolic Blood Pressures in Dispensary Series by Age Groups and by Sex*

	Males		Females		Composite	
Age Groups	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
35-40	135	86	129	83	132	84
40-45	136	89	134	85	135	87
45-50	144	85	139	82	142	84
50-55	135	82	131	79	134	81
55-60	151	90	145	87	149	89
60-65	148	87	145	83	147	85
65-70	154	86	154	84	155	85
70-75	155	86	152	82	154	84
75 plus	156	96	160	94	158	96

TABLE 3.—*Mean Systolic and Diastolic Blood Pressures in Hospital Series by Sex and by Age Groups*

	Males		Females		Composite	
Age Groups	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
35-40	127	78	123	75	124	76
40-45	123	85	121	80	120	83
45-50	155	86	149	78	152	82
50-55	151	88	145	86	147	87
55-60	155	86	152	85	153	85
60-65	151	86	154	88	152	87
65-70	146	85	140	79	143	82
70-75	155	93	150	89	152	91
75 plus	148	98	142	86	146	87

In table 1 the age group distribution for these three series, as well as for the diabetic series, is given. In tables 2, 3 and 4 the average systolic and diastolic blood pressures are shown, arranged according to sex and according to age groups.

In the 500 clinical cases of diabetes mellitus, 408 of the patients were 35 years or older; only the older age groups will be used in the statistical study which is to follow. Of these 408 patients, 356 received more than one observation on the blood pressure. If more than one reading was made, the mean pressure was taken in computing the statistical data given in the present paper. All the observations were made according to the methods described except that in this group the

readings were made by several different persons. The blood pressures of this group are shown in table 5, arranged according to sex and age distribution.

In all four groups there were more females than males, and the proportion was greatest in the diabetic series, the ratio being 5 : 3.

In table 2 it will be seen that in the dispensary series the mean systolic blood pressure of the men was greater than that of the women in all age groups except the 65 to 70 and 75 year groups, whereas the diastolic pressures of the males were higher in all age groups. In the hospital series, as shown in table 3, both the systolic and the

TABLE 4.—*Mean Systolic and Diastolic Blood Pressures in Normal Series by Sex and by Age Groups*

	Males		Females		Composite	
Age Groups	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
35-40	124	83	118	77	120	79
40-45	130	80	126	76	129	79
45-50	135	84	133	82	134	83
50-55	133	85	130	82	131	83
55-60	142	91	137	86	139	88
60-65	145	87	136	79	141	83
65-70	139	82	135	78	137	80
70-75	148	90	141	82	144	87
75 plus	140	80	131	69	135	75

TABLE 5.—*Mean Systolic and Diastolic Blood Pressures in Diabetic Series by Sex and by Age Groups*

	Males		Females		Composite	
Age Groups	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
35-40	112	72	129	76	118	73
40-45	118	71	138	85	125	76
45-50	116	76	151	84	137	81
50-55	138	82	155	86	144	83
55-60	135	81	159	85	149	82
60-65	148	89	158	82	152	85
65-70	138	84	178	89	154	85
70-75	151	83	169	86	159	84
75 plus	176	96	120	69	136	76

diastolic blood pressures were higher in the case of the women in the 60 to 65 year age group, while the pressures of the men were higher in all the other age groups. In the normal series, as shown in table 4, both the systolic and the diastolic blood pressures were higher in the males in all age groups. In the diabetic series, as shown in table 5, it was found that the systolic blood pressures were higher in the women than in the men after the age of 35, with the exception of the 75 year age group, and the diastolic pressures of the women were higher than the diastolic blood pressure in the men in the corresponding age groups, with the exception of the 60 to 65 year age group, in which the mean diastolic pressure was higher in the men than that in the women.

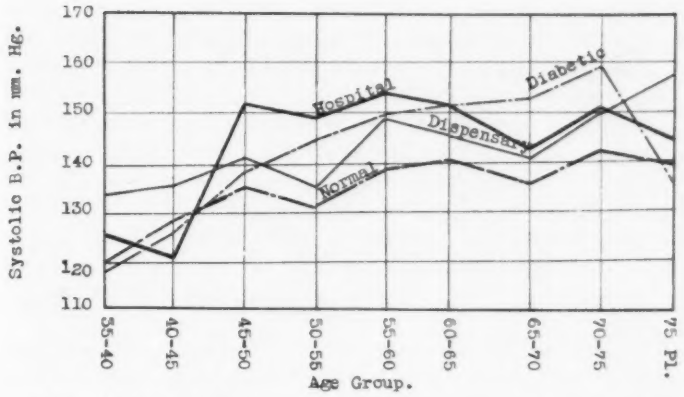

Chart 1.—Curves for the mean systolic blood pressure of the different series by age groups.

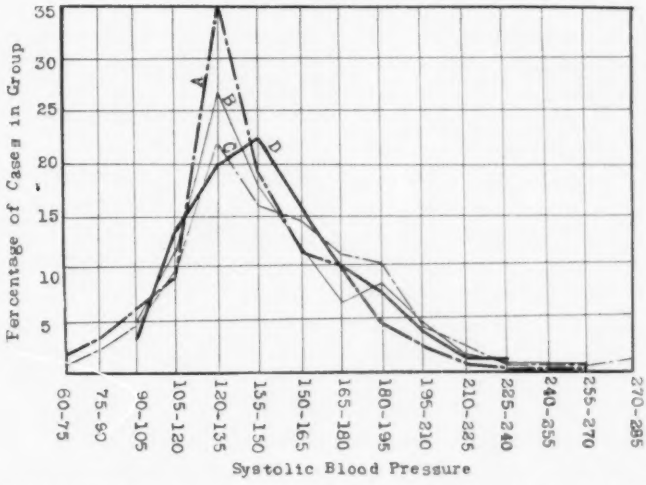

Chart 2.—Distribution of cases according to the systolic blood pressure (15 mm. groups) in persons over 35. *A* indicates the curve for the normal series; *B*, for the hospital series; *C*, for the dispensary series, and *D*, for the diabetic series.

If tables 2, 3, 4 and 5 are compared, it is seen that the mean systolic blood pressure was higher in the diabetic series than that of any other series in only two age groups, the 65 to 70 and the 70 to 75 year groups, while the diastolic pressure was not higher in the diabetic series than that of any other series in any single age group. It was also found that in the normal series the systolic pressures were lower than those of any other group of cases after the age of 45, whereas the diastolic pressures were lower in the 60 to 65, 65 to 70 and 75 year age groups. The mean systolic blood pressures in the different series are represented by age groups in chart 1.

Arranging the cases in 15 mm. groups according to their systolic blood pressures, so as to obtain smoother curves, it was found that the peak of the curve for the diabetic series came in the 135 to 150 mm.

TABLE 6.—*Percentage of Cases in Each Series by Age Groups with Systolic Pressure of 150 mm. or More, and with Diastolic Pressure of 100 mm. or More*

	Normal		Dispensary		Hospital		Diabetic	
Age Groups	Systolic 150 Plus	Diastolic 100 Plus	Systolic 150 Plus	Diastolic 100 Plus	Systolic 150 Plus	Diastolic 100 Plus	Systolic 150 Plus	Diastolic 100 Plus
35-40	1.8	1.8	20.9	16.3	3.6	5.4	5.5	....
40-45	19.0	2.1	25.5	18.6	26.1	17.4	25.8	20.0
45-50	29.1	18.2	23.2	16.3	38.1	23.8	29.9	15.9
50-55	25.5	9.9	47.5	4.6	40.6	24.7	33.6	19.5
55-60	36.4	18.2	45.5	27.0	48.1	32.7	45.0	22.6
60-65	40.0	6.9	51.2	18.6	47.9	21.8	52.0	12.3
65-70	29.1	5.4	55.5	16.2	50.0	18.5	58.0	25.8
70-75	32.2	13.6	57.2	35.6	51.2	21.9	77.0	18.2
75 plus	30.0	11.6	54.6	30.3	41.9	18.6	58.1	12.5

group, whereas the peaks of all the other curves fell in the 120 to 135 mm. group (chart 2). It was also noted that subsequently the curve for the diabetic series was higher than any other curve, until it was finally crossed by the curve for the dispensary series at about 160 mm. of mercury.

In table 6 the percentage of cases in each group with a systolic blood pressure of 150 mm. or more, and with a diastolic blood pressure of 100 mm. or more, is shown according to age groups. From the study of this table it is evident that in the four highest age groups a greater percentage of cases having systolic blood pressures of 150 mm. or more was found in the diabetic series than in any other series, while only in the 65 to 70 year age group was the percentage of cases having a diastolic pressure of 100 mm. or more higher in the diabetic series than in any other series.

Investigation of the pulse pressure is an important consideration in such a disease as diabetes mellitus, in which arteriosclerosis is a too

frequent complication to be overlooked. Fahr [55] showed that "arteriosclerosis only increases the work of the heart insofar as it necessitates increased blood pressure." With an elevation of systolic and of diastolic blood pressure, more work is required of the heart to expel a given volume of blood than with normal systolic and diastolic blood pressures, as has been shown by Bramwell, Downing and Hill.[56] Under these conditions a higher pulse pressure is required. In the present series of cases it was found that the pulse pressure was higher in the diabetic series than in any other group of cases in the following age groups: 50 to 55, 60 to 65 and 70 to 75.

In curves representing the distribution of cases in the different age groups it was found that the curves were asymmetrical. However, by the use of the formula given by Karl Pearson, the skewness of the curves was estimated for the different series of cases. The values were found to be as follows: dispensary series, 0.276; hospital series, 0.319; normal series, 0.045, and diabetic series, 0.004. Thus, it is seen that the age distribution of the cases was most asymmetrical in the dispensary and hospital series.

The mean systolic blood pressure for the entire group in each series was determined, regardless of age and sex, and the following values were found: dispensary series, 143 mm.; hospital series, 144 mm.; normal series, 136 mm., and diabetic series, 144 mm. The mode for the different series was: dispensary, 132.5 mm.; hospital, 132.5 mm.; normal, 122.5 mm., and diabetic, 142.5 mm. The median was as follows: dispensary, 142.5 mm.; hospital, 137.5 mm.; normal, 132.5 mm., and diabetic, 142.5 mm. Thus, the mean systolic blood pressure for the dispensary, hospital and diabetic series was practically the same, whereas that for the normal series was considerably less than that of any other group.

Before proceeding further into a statistical consideration of this problem it will be necessary to calculate the standard deviation for systolic blood pressure in each of the four groups of cases, since further determinations will involve a consideration of these values. In statistical work the root-mean square of a series of numbers is the square root of the arithmetic mean of their squares. In applying this formula to the systolic blood pressures the following values for the standard deviation were found:

Dispensary series	38.0
Hospital series	32.9
Normal series	29.6
Diabetic series	44.2

55. Fahr, G.: Proc. Soc. Exper. Biol. & Med. **24**:405, 1926.

56. Bramwell, J. C.; Downing, A. C., and Hill, A. V.: Heart **10**:289, 1923. Bramwell, J. C., and Hill, A. V.: Lancet **1**:891, 1922.

Having obtained the standard deviation for the systolic blood pressures, the probable error for each of these values remains to be determined. These are as follows:

Dispensary series	38.0 ± 1.32
Hospital series	32.9 ± 1.01
Normal series	29.6 ± 0.89
Diabetic series	44.2 ± 1.47

From the data thus far obtained the coefficient of variability was calculated. This is the ratio of the standard deviation to the arithmetic mean, and is usually expressed as a percentage. These values are shown in the following:

Dispensary series	26.6
Hospital series	22.9
Normal series	21.8
Diabetic series	30.7

From the data given the significance of these figures can be determined. In statistical work the significance is based on the ratio of the difference of the means to the probable error of the difference. The ratios are:

Diabetic and hospital series	0.0
Diabetic and dispensary series	0.5
Diabetic and normal series	4.7
Normal and hospital series	5.9
Normal and dispensary series	4.4

Statisticians are accustomed to take arbitrarily the ratio of 2.5 or 3, or more, as a significant value. Hence, the ratio of the difference of the means to the probable error of the difference was significant in the normal and diabetic series, in the normal and hospital series and in the normal and dispensary series.

Thus far the standard deviation and the probable errors for the systolic blood pressures for the entire groups have been studied. In computing the standard deviation and the probable errors of the mean systolic blood pressures for each age group in the normal and in the diabetic series, the ratio of the difference of the means to the probable error of the difference of the means was found to have a significant value (2.5 or more) in the following age groups: 50 to 55, 55 to 60, 60 to 65, 65 to 70 and 70 to 75. The ratio was not significant in the younger age groups, nor was it significant in the 75 year age group. The discrepancy in the latter case was probably due to the small number of cases in this group.

It is obvious that some attempt should be made to correlate age and systolic blood pressure in the different series of cases. The correlation was positive in all the different groups of cases, and was highest in the normal series, while it was lowest in the dispensary series and in the hospital series. The values are as follows:

Dispensary series	0.0409
Hospital series	0.0755
Normal series	0.2659
Diabetic series	0.2238

The probable error of the coefficient of correlation of age and systolic blood pressure was determined in the normal and in the diabetic series, and these values are:

Normal series	0.2659 ± 0.0277
Diabetic series	0.2238 ± 0.0316

It was found, therefore, that the difference of the coefficients of correlation bore a ratio to the probable error of the difference of 1 : 10, which is a highly significant value.

From the data given straight line curves were plotted for the different groups of cases, by the use of a regression formula. These curves are shown in chart 3. It is seen that the curves for the dispensary and hospital series show little elevation, owing to the low correlation between age and systolic blood pressure. It is also evident that the curve for the normal group is definitely lower than any of the other curves, and that after the age of 60 the curve for the diabetic series is higher than any other curve.

In addition to the study of blood pressure, it is pertinent that other evidence of hypertension be sought. It is conceivable that the blood pressure may have been within normal limits at the time the observations were made, although the person may have suffered from hypertension at some earlier period. It is known that changes in the small vessels are a more reliable index to hypertension than are changes in the larger vessels. Fortunately, the ocular fundi afford an excellent opportunity for the study of such vessels.

In the diabetic series the eyegrounds were examined in 386, or 77 per cent, of the cases. The points observed in these examinations were: abnormal tortuosity of the vessels, caliber changes of the vessels, nicking at the arteriovenous junctions and areas of old or of recent hemorrhage. In 189 cases (38 per cent), some degree of vascular change was noted. Such cases were more frequent in the older age groups, although a few of the cases in the younger age groups also revealed some vascular injury.

In the diabetic series only 14 patients (2.8 per cent) were thought to have renal disease. Of the 500 cases, 239 (48 per cent) showed arteriosclerosis of varying degree.

No attempt has been made to determine the correlation between systolic blood pressure and increase in body weight above normal, since the weights were not available in the diabetic series.

In addition to the clinical series discussed, a group of diabetic cases coming to necropsy has been studied. Here the points of chief concern were the weight of the heart and kidneys and the cardiovascular complications.

As a standard for comparison, the weight of the heart in 1,000 consecutive necropsies was taken, the cases being arranged according

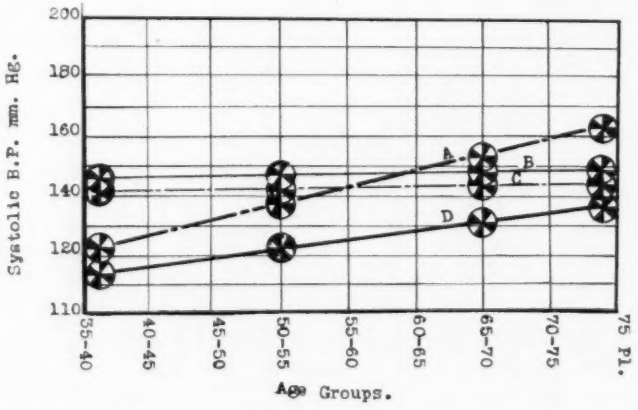

Chart 3.—Straight line curves for the systolic pressures. *A* indicates the curve for the diabetic series; *B*, for the hospital series; *C*, for the dispensary series, and *D*, for the normal series.

to five-year age groups and according to sex. The mean values obtained showed that the heart tended to increase in size to about the age of 60, after which it decreased slightly. The highest mean weight in the men was 384 Gm., at the age of from 60 to 65, while the highest value in the women was 366 Gm., at the age of from 55 to 60.

In the study of 104 cases of diabetes mellitus coming to postmortem examination all cases showing vascular injury were excluded, since certain types of valvular disease may give rise to hypertrophy of the heart, there being no associated increase in systolic blood pressure. Of course, I was aware that other conditions than hypertension and valvular disease can cause hypertrophy of the heart. After calculating the mean weight, according to sex and also according to five-year age

groups, it was found that the weight of the heart of the men in the diabetic series exceeded that of the men in the control series after the 50 to 55 years age group, whereas the weight of the heart of the women in the diabetic series exceeded that of the women in the control series after the age of 65 to 70. When both sexes were included in this comparison, it was found that the curve representing the diabetic series was higher than that representing the control series after the age of 50 to 55, as shown in chart 4.

The weight of the kidneys was also studied, and a comparison made with the weight in a control group, the latter being based on the weight of the kidneys in 650 consecutive necropsies. It was found that the kidneys in the diabetic series weighed slightly more than those

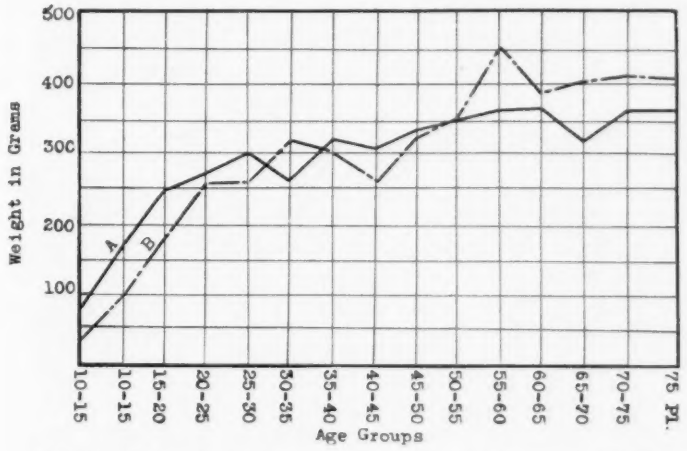

Chart 4.—Curves for the weight of the heart for both sexes. *A* indicates the curve for the normal series; *B*, for the diabetic series.

in the control series. If hypertension were present in the diabetic cases, it might be expected that the kidneys in these cases would be the seat of arteriolar disease, and would be smaller than those in the control series. It should be remembered, however, that there is often an accompanying nephrosis, and in these cases the kidneys tend to be somewhat larger than normal.

The percentage of cases in which diagnoses pertinent to cardiovascular disease were made in the diabetic series is shown in the following tabulation.

General arteriosclerosis	32
Coronary sclerosis	22
Hypertrophy of the heart	21

Edema of the lungs	21
Gangrene of the extremities	19
Arteriosclerosis of the kidney	17
Chronic passive congestion of various viscera	15
Hydrothorax	13
Fibrous myocardium	10
Generalized edema	8
Ascites	6

SUMMARY

The blood pressure in a clinical series of cases of diabetes mellitus is compared with the blood pressure in a series of dispensary cases, with that in a series of hospital cases and finally, with that in a series of so-called normal persons. These figures are subjected to a statistical analysis.

A necropsy series of diabetic cases is also studied, and the weight of the heart and the kidneys is compared with the weight in a control series.

In elderly diabetic patients the systolic blood pressure is slightly higher than that of patients seen in a dispensary series or in a hospital series, and is considerably higher than the blood pressure in normal persons of the same age group.

Although the mean systolic blood pressure in the diabetic series is not essentially different from that in either the dispensary series or the hospital series, there is a greater tendency to a slight elevation of the systolic blood pressure in diabetic persons than in those in the other series mentioned, as is shown by a statistical study.

THE RATE OF GLYCOLYSIS IN ERYTHREMIA (POLYCYTHEMIA VERA) *

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AND
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In a recent article by Falcon-Lesses,[1] the author applied the observations of Warburg and Murphy and Hawkins on glycolysis in malignant disease to the apparently similar problem of glycolysis in leukemic blood. He found that, whereas in normal persons glycolysis in blood containing not more than 100 mg. of dextrose per hundred cubic centimeters is completed in about six hours, in the blood of patients with myelogenous leukemia the process was from two to three times as rapid, being complete in from one to four hours.

In seeking some explanation of the mechanism of this process, Falcon-Lesses made observations in two other cases showing abnormal conditions of the blood, one of polycythemia with a red cell count of 9,505,000 and a white cell count of 25,775 and the other a case of pernicious anemia with a red cell count of 2,800,000 and a white cell count of 4,000. The rate of glycolysis in the erythremic blood was "considerably accelerated," being complete in less than four hours. The rate of glycolysis in the blood of the patient with pernicious anemia was slower than in the normal blood. Falcon-Lesses suggested that the increase of white cells in the erythremic blood may be in part at least responsible for the increased rate but that "it seems more probable that the rates were in some manner dependent on the fact that the blood of one patient contains 6,000,000 more red cells per cubic millimeter than that of the other." This surmise seems logical, since it is known that glycolysis in normal blood is in the main a function of the intact red cells.

Having under observation at present two cases of erythremia, we thought it of interest to determine the rate of glycolysis under varying conditions, in particular to observe possible changes after the red blood cells had been brought down to approximately normal number by the administration of phenylhydrazine. One of these cases (no. 2) seemed especially suitable for our purpose, since it belongs to the rather unusual type of erythremia in which the white cells are not increased, either

* Submitted for publication, May 21, 1929.

* From the Medical Service of the Jewish Hospital.

1. Falcon-Lesses, M.: Glycolysis in Normal and in Leukemic Blood, Arch. Int. Med. **39**:412 (March) 1928.

originally or after the administration of phenylhydrazine, so that the question of glycolytic effect of the nucleated cells should not enter.

The glycolysis experiments were carried out with defibrinated blood in order to preclude the inhibiting effect of the common anticoagulants. Immediately after defibrination, the blood samples were quickly warmed to 37 C. in a water bath of constant temperature. Sedimentation of the cells was prevented by gentle agitation of the samples. The duration of the observation in no case exceeded a period of three hours, rendering special precautions of aseptic handling unnecessary.

REPORT OF CASES

CASE 1.—Mrs. A., aged 59, has been under observation because of erythremia since November, 1922. She had had a number of courses of phenylhydrazine since that date but none since December, 1926. On May 16, 1928, the blood showed the following: hemoglobin (Sahli), 116 per cent; red cells, 7,950,000; white cells, 16,100. The rate of glycolysis is shown in table 1.

TABLE 1.—*Rate of Glycolysis in Case 1 on May 16*

Time of Incubation, Minutes	Sugar Content, Mg. per 100 cc.	Loss of Sugar, Mg. per 100 cc.
0	97	0
30	59	38
60	31	66
120	15	82

TABLE 2.—*Rate of Glycolysis in Case 1 on June 27*

Time of Incubation, Minutes	Sugar Content, Mg. per 100 cc.	Loss of Sugar, Mg. per 100 cc.
0	89	0
30	58	31
60	15	74

The whole of the dextrose was cleaved in less than two hours, and it seems probable that during the second hour considerably more would have been broken down if it had been present. (The 15 mg. per hundred cubic centimeters found at the end of the second hour represents reducing substances other than sugar.[2]) Thus in judging the rate of glycolysis, one has to depend on the observation in the first hour, which shows a rate of 66 mg. per hundred cubic centimeters of blood per hour.

The patient was then given phenylhydrazine, 0.06 Gm. three times daily, until on June 20, 1928, she had taken a total of 3.4 Gm., and the blood showed: hemoglobin, 93 per cent; red blood cells, 5,120,000, and white blood cells, 28,800. A week later, without further administration of the drug, the blood showed: hemoglobin, 72 per cent; red blood cells, 3,600,000; white cells, 29,000. Blood was at this time again taken for determination of the rate of glycolysis.

2. Somogyi, M.: Reducing Non-Sugars and True Sugar in Human Blood, J. Biol. Chem. **75**:33, 1927.

The loss of sugar by glycolysis in this sample was 74 mg. in one hour, the remaining 15 mg. per hundred cubic centimeters again representing reducing substances other than sugar. Whereas the brief duration of the process does not permit the conclusion that the rate was higher in this case than in the first, it is fair to concede that it was at least not lower, a striking result, considering the difference of more than 100 per cent in the red counts of the two specimens.

Case 2.—J. G., a man, aged 49, was first seen on Dec. 19, 1927, at which time his blood showed: hemoglobin, 131 per cent; red blood cells, 8,900,000, and white blood cells, 6,400. Many subsequent counts during and after the administration of phenylhydrazine showed an average white cell count of about 8,000. A few counts were between 10,000 and 11,000.

On January 26, the blood showed: red blood cells, 7,990,000; white blood cells, 7,600. The rate of glycolysis is shown in table 3.

Table 3.—*Rate of Glycolysis in Case 2 on January 26*

Time of Incubation, Minutes	Sugar Content, Mg. per 100 cc.	Loss of Sugar, Mg. per 100 cc.
0	115	0
60	97	18
120	59	56
180	25	90

Table 4.—*Rate of Glycolysis in Case 2 on March 9*

Time of Incubation, Minutes	Sugar Content, Mg. per 100 cc.	Loss of Sugar, Mg. per 100 cc.
0	112	0
30	94	18
60	76	36
90	57	55
120	39	73

The loss in dextrose was 90 mg. in three hours, or 30 mg. per hundred cubic centimeters of blood per hour, a rate about twice as high as in normal blood.

On February 1, the patient was given 0.05 Gm. of phenylhydrazine three times daily; this dosage was later increased to 0.06 and 0.07 Gm. three times daily. He did not remain under rigid observation and was probably a bit irregular in taking the drug but by March 9 had received a total of 5 Gm., when it was discontinued. The count at this time showed: hemoglobin, 65 per cent; red blood cells, 4,080,000, and white blood cells, 8,400; the rate of glycolysis is shown in table 4.

The rate of glycolysis in this determination was 36 mg. per hundred cubic centimeters of blood per hour, again slightly higher than it was before the red cell count had been decreased by approximately one half through the administration of phenylhydrazine.

Since in the instance of myelogenous leukemia it has been suggested on the basis of considerable evidence that the increased rate of glycolysis may be due to the presence of an increased proportion of young, newly formed white blood cells, we extended our investigation in this direction by repeating our experiments in case 2, with the addition of observations on the proportion of reticulated cells.

On Jan. 14, 1929, the blood picture was: hemoglobin, 160 per cent; red blood cells, 9,800,000; white blood cells, 8,720, and reticulated cells, 0.3 per cent. The rate of glycolysis is shown in table 5.

This represents a rate of glycolysis of 31 mg. per hundred cubic centimeters per hour. The patient was then given 0.07 Gm. of phenylhydrazine three times daily until by Feb. 15, 1929, the rather large total of 6.8 Gm. had been taken. On this date the hemoglobin was 90 per cent and the red blood cells 5,000,000. The administration of the drug was discontinued, and five days later, on February

TABLE 5.—*Rate of Glycolysis in Case 2 on January 14*

Time of Incubation, Minutes	Sugar Content, Mg. per 100 cc.	Loss of Sugar, Mg. per 100 cc.
0	105	0
30	88	17
60	73	32
120	43	62
150	28	77

TABLE 6.—*Rate of Glycolysis in Case 2 on February 20*

Time of Incubation, Minutes	Sugar Content, Mg. per 100 cc.	Loss of Sugar, Mg. per 100 cc.
0	80	0
30	63	17
60	47	33
90	31	49
120	18	62

TABLE 7.—*Rate of Glycolysis in Case 2 on March 6*

Time of Incubation, Minutes	Sugar Content, Mg. per 100 cc.	Loss of Sugar, Mg. per 100 cc.
0	94	0
60	59	35
90	45	49
120	30	64
150	13	81

20, the following observations were recorded: red blood cells, 4,750,000; white blood cells, 12,500, and reticulated cells, 2.7 per cent; the rate of glycolysis is shown in table 6.

This table shows a rate of glycolysis of 31 mg. per hundred cubic centimeters per hour, a value virtually identical with the one obtained before the reduction by one half of the red blood cells.

On March 6, the patient having received no phenylhydrazine meanwhile, this examination was repeated with the following result: red blood cells, 4,470,000; white blood cells, 9,700, and reticulated red cells, 1 per cent; the rate of glycolysis is shown in table 7.

The hourly rate of glycolysis in this instance was 32 mg. per hundred cubic centimeters, or the same as in the preceding experiment. It should be remem-

bered that in the last two experiments the blood filtrates for sugar determinations were prepared by a new zinc-precipitation method,[3] which accounts for the fact that the initial level of the blood sugar is about 20 mg. per hundred cubic centimeters lower than in the previous experiments on the same patient. All sugar determinations were carried out by the modified Shaffer-Hartmann method.

SUMMARY

1. The blood of patients with erythremia (polycythemia vera) shows a greatly increased rate of glycolysis.

2. This increased rate is independent of the red cell count as influenced by phenylhydrazine, and shows no direct relation to the proportion of young red cells, when the reticulated count is used as an index of such cells.

3. The increased rate of glycolysis in the usual case of erythremia is not dependent on the increased white count since the increased rate is also present with a low white cell count.

3. Somogyi, M.: A Method for the Preparation of Blood Filtrates for Analysis, Proc. Soc. Exper. Biol. & Med. **26**:353, 1929.

THE BROMSULPHALEIN HEPATIC FUNCTION TEST

REPORT OF A SERIES OF TESTS *

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Each of the numerous functions of the liver has been used, at one time or another, as an index to the function of the whole organ. The ideal test by which a quantitative estimation of one function of the liver may thereby indicate the degree of impairment in disease has not as yet been discovered. Although this criticism may be directed against any of the tests in use, it is not constructive. Only by repeated trial and experimentation can one hope to learn which tests are best suited to estimate the function of the organ in any given disease.

Perhaps the most infallible test is the clinical observation of jaundice, and of the concomitant changes in the excreta, namely, dark urine and clay-colored stools. Along with these clinical tests may be listed the laboratory tests which determine the amount of bilirubin in the blood, chief of which are the icterus index and the van den Bergh test. Shattuck, Brown and Preston,[1] in 1925, considered the icterus index as the most useful of all tests for this organ, but also stated that the Rosenthal test was of greater value in cirrhosis and malignancy, that it served as a guide to arsenical treatment in syphilis and that its greatest value was in hepatic disease without jaundice. Snell and Rowntree,[2] in 1928, considered that serum bilirubin was best studied by the van den Bergh test, although the icterus index afforded information of clinical significance.

Dextrose and fructose tolerance tests, estimation of bile and of dye in the feces and urine, estimation of bile and dye in the duodenal contents, together with many other tests, have been used. Much has been written and many cases reported with regard to the use of phenoltetrachlorphthalein. This dye given intravenously is normally removed from the blood in fifteen minutes, with the exception of from 3 to 5 per cent, and is all removed at the end of an hour. Retention is considered to indicate impaired hepatic function. This dye was irritant, caused occasional thrombosis and some severe local and general reaction, even though it was well diluted and the vein was well washed. In 1925,

* Submitted for publication, May 25, 1929.

* From the Laboratory Service, Letterman General Hospital.

1. Shattuck, H. F.; Brown, J. C., and Preston, M. P.: Am. J. M. Sc. **170**: 510, 1925.

2. Snell, A. M., and Rowntree, L. G.: Am. J. Surg. **4**:206 (Feb.) 1928.

Rosenthal and White [3] introduced a new dye which they had used experimentally in rabbits and then applied to clinical use. This was bromsulphalein (phenoltetrabromphthalein sodium sulphonate), and in twenty-five normal cases they found from 20 to 50 per cent of the dye remaining in the serum five minutes after intravenous injection, while there was none, or but a faint trace, remaining at the end of thirty minutes. The average five minute retention in the normal subjects was 35 per cent.

Maurer and Gatewood [4] had just previously quoted LeCount as suggesting the possibility of changes in the liver from the presence of any halogenated compound in concentrated form, due to the splitting off of the halogen acid in free form by the active metabolism of the liver with resultant acute necrosis. In reply to this, Rosenthal and White, in a footnote to their article just mentioned, said: "The statement that the quantity of tetrachlorphthalein used may damage the liver has no foundation in a large amount of experimental work, and seems chemically impossible on a basis of the halogen content."

Greene, Snell, Walters [5] and others, in reporting a series of studies on hepatic function tests in 1925, stressed the parallelism between the bilirubin content and dye retention in hepatic disorders. In a later paper, Greene, McVicar, Rowntree and Walters [6] stated: "We have stressed the close parallelism between the behavior of the serum bilirubin and the phenoltetrachlorphthalein in this series of cases. That the two readings do not have the same significance is shown by the behavior during the later portion of the recovery period." This point is also further borne out by the difference between the two tests in cirrhosis and carcinoma without jaundice.

Since the introduction of the new dye, bromsulphalein, the older dye has been generally discarded. A smaller quantity of bromsulphalein may be used yet a greater concentration results in the blood. No thromboses have been reported (except one in a case of polycythemia vera),[7] nor have there been any appreciable local or general reactions. Direct injection of a 5 per cent solution without further dilution is used, and samples for reading are taken at five and thirty minute intervals, thus simplifying the procedure.

Major William S. Shields was instrumental both in the use of tetrachlorphthalein and in the change to bromsulphalein at the Letterman

3. Rosenthal, S. M., and White, E. C.: Clinical Application of Bromsulphalein Test for Hepatic Function, J. A. M. A. **84**:1112 (April 11) 1925.

4. Maurer, S., and Gatewood, L. C.: Phenoltetrachlorphthalein Liver Function Test, J. A. M. A. **84**:935 (March 28) 1925.

5. Greene, C. H.; Snell, A. M., and Walters, W.: Diseases of the Liver, Arch. Int. Med. **36**:248 (Aug.) 1925.

6. Greene, C. H.; McVicar, C. S.; Rowntree, L. G., and Walters, W.: Diseases of the Liver, Arch. Int. Med. **36**:418 (Sept.) 1925.

7. Serby, A. M., and Bloch, L.: Am. J. M. Sc. **176**:367 (Sept.) 1928.

General Hospital, and in February, 1928, use was made of the new dye. Major Shields and Captain Douglas H. Mebane have selected most of the cases in which the test was applied, generally, I believe, with a view to study of the individual case, but always with an open mind as to the conclusions to be drawn pending a closer study of the test. Primarily, the first object in collecting the data in this series was to determine whether or not the five minute sample was of sufficient value to warrant its routine collection. To decide this question, it has been necessary to classify and group all cases in which the test was used, and the data thereby collected are presented for information. Apparent points of interest have been emphasized and some suggested conclusions drawn.

PROCEDURE

The test has been performed as follows:

(*a*) The patient is prepared merely by having no breakfast. This is done to avoid the occasional cloudy serum obtained after a meal. In the future I expect to allow dry, unbuttered toast and coffee without cream.

(*b*) The patient's weight (stripped) is obtained, and this, divided by 55, gives the number of cubic centimeters of a 5 per cent solution of bromsulphalein to be injected. This is based on a dosage of 2 mg. per kilogram of body weight.

(*c*) The correct amount is injected into a large vein at the elbow, a 5 cc. syringe graduated in tenths being used, and the injection completed in approximately one minute. At the beginning of the injection a stopwatch is started and the interval of injection noted.

(*d*) Five minutes after completion of the injection, a sample of blood is withdrawn from a vein of the other arm, to avoid possible residual dye.

(*e*) Another sample is withdrawn thirty minutes after completion of the injection.

(*f*) The blood is allowed to clot, the coagulum gently loosened, the sample centrifugated and the clear serum removed.

(*g*) To a portion of one sample of the serum a drop of 5 per cent hydrochloric acid is added and to another portion, three drops of a 10 per cent solution of sodium hydroxide. The other sample is treated only with the hydroxide. An alkaline tube is thus prepared for each sample; only one acid tube is required for each test.

(*h*) The acid tube is used as a serum control and behind it, in a comparator block, are placed the standards, as required. Behind each alkaline tube is a tube of distilled water. The tubes of permanent standards, as supplied by Hynson, Westcott and Dunning, are used to match the sample as nearly as possible. The experimenters interpolate when it is thought necessary.

The average normal reading, according to Rosenthal,[3] is 35 per cent at five minutes and zero at thirty minutes. In a recent number of the *American Journal of Medical Science*, Serby and Bloch[7] reported a series in which they used 35 as the upper limit of normal, but Rosenthal reported his normals to range between 20 and 50. Attention is called to the figures in the following tables which bear on this subject.

During approximately seven months (February 10 to September 13), 137 Rosenthal tests were performed, the bromsulphalein dye being used. In the 137 tests performed, no five minute sample could be obtained (or was not desired) in ten tests on nine persons. These tests were not included in the tables, except for three performed on patients whose other tests were complete. This gives a total of 130 tests in 100 cases. No effort was made at intensive study of these cases, other than as desired by the clinician. The laboratory personnel were generally uninformed as to the character of each case, and much of the data presented have been abstracted from charts after discharge of the patients. However, when a question of proper classification arose, an effort was made to avoid favoring the test by consultation with Captain Mebane, on whose service most of the patients were studied. From

TABLE 1.—*Bromsulphalein Tests at Letterman General Hospital from Feb. 10 to Sept. 13, 1928*

Group	Cases	Tests
Hepatitis, nonsyphilitic and nonarsenical	5	16
Hepatitis, syphilitic and arsenical	10	19
Cancer	7	9
Cirrhosis:		
Atrophic	1	2
Unclassified	5	5
Hypertrophic	19	25
Cholecystitis and cholelithiasis	11	11
Cholangeitis	3	3
Nonhepatic	40	41
	101	131
Correction for one case duplicated under malignancy and cirrhosis, hypertrophic	1	1
Total	100	130

the data recorded and his recollection of the case, it was then decided in what group such cases belonged. No general reaction occurred in any of the patients to whom the dye was administered. In a few cases accidental subcutaneous leakage of the dye was unavoidable, but no local reaction or discomfort followed. Thrombosis after administration of bromsulphalein has not been observed at this hospital.

In table 1, the cases and tests are grouped to give a general idea as to the diseases studied.

In table 2 are shown two groups of tests: (1) those giving readings of 50 per cent or under at five minutes, and zero at thirty minutes, and (2) those giving readings which indicate a retention of dye at both intervals. Thirty-seven tests showed no retention above normal, the average five minute reading being 38, which is close to Rosenthal's average five minute reading of 35. Twenty of these tests were above 35 and sixteen of the twenty above 40. Seventeen were 35 or less. The distribution of these cases with regard to diagnosis will be shown later and perhaps further light thrown on these figures.

Fifty-five tests showed a percentage of dye retention in both samples above the accepted normal. In this table the five minute column gives the amount above the accepted maximum normal of 50. For instance,

TABLE 2.—*Tests Showing No Retention Above Normal at Five Minute Reading and Retention Above Normal at Both Five and Thirty Minute Readings*

	No Retention Above Normal		Retention Above Normal at Both Intervals		
				Percentage Over Normal	
Number	Test Number	5 Minute Reading	Test Number	5 Minutes	30 Minutes
1	1	45	5	5	15
2	2	45	7	50+	45
3	11	35	8	5	2
4	12	38	10	40	15
5	13	35	14	5	10
6	15	50	19	28	60
7	16	40	28	20	3
8	17	50	29	40	10
9	20	35	32	10	22
10	22	35	34	35	5
11	23	35	39	40	35
12	24	38	47	35	18
13	25	35	48	50+	85
14	30	45	49	50+	70
15	31	35	54	35	30
16	33	30	55	50+	100
17	35	22	57	10	3
18	36	25	58	5	8
19	40	25	59	5	15
20	41	42	63	10	12
21	44	48	64	40	38
22	45	43	65	20	5
23	50	25	67	22	4
24	51	20	68	50+	70
25	53	30	69	50+	57
26	56	35	70	30	35
27	60	50	71	5	8
28	61	42	73	50+	95
29	72	50	74	50	38
30	81	32	75	38	23
31	89	20	77	30	4
32	93	38	83	2	8
33	128	50	84	35	15
34	129	45	85	50	58
35	135	45	87	35	8
36	136	40	91	50+	100
37	137	45	94	2	Trace
38	...	..	96	40	10
39	...	..	97	50+	8
40	...	..	101	10	3
41	...	..	102	50+	60
42	...	..	104	10	35
43	...	..	105	2	15
44	...	..	106	45	8
45	...	..	108	45	8
46	...	..	109	5	8
47	...	..	111	10	2
48	...	..	113	50+	50
49	...	..	116	50+	100
50	...	..	117	50+	100
51	...	..	121	35	35
52	...	..	125	50+	50+
53	...	..	127	10	10
54	...	..	131	40	40
55	...	..	133	30	30
Total		1,408			

Average 5 minute reading, 38

no. 4 (test 10) gave readings of 90 and 15, and is recorded as 40 above normal at five minutes and 15 above normal at thirty minutes.

It will be noted that fourteen tests show a 50 plus five minute retention above normal or the readings as reported were 100 per cent plus.

If the standard maximum concentration is correct, as computed by Rosenthal,[1] i. e., 2 mg. of dye per kilogram of body weight representing 4 mg. per hundred cubic centimeters of blood at highest concentration, then it would seem impossible to obtain such a reading, for this is the concentration of dye represented in the 100 per cent tube in the set of standards. I have theorized on this point seeking an explanation, but so far have failed. They have all occurred in cases of hepatitis, cholangeitis or malignancy—in cases with severe injury of the liver. In one of these cases the same reading was made at thirty minute intervals, though the second concentration was appreciably lighter than the first (about 160 and 120 as estimated). Three times the thirty minute concentration was read 100, once 95, once 85, thrice 70, once 60, once 57, once 50, once 45 and once 8 per cent. The last was during the improvement of a patient who suffered from a slight relapse. The patients were usually severely jaundiced, but in the test giving only 8 per cent retention at thirty minutes there was less than 0.8 van den Bergh unit present in the blood removed when the Rosenthal test was performed. Further study of this group of tests showing retention at both intervals has not been made except in connection with their clinical grouping.

Serby and Bloch, already quoted, also reported six cases in which a five minute retention was recorded as 100 per cent plus, five of these being cases of carcinoma of the head of the pancreas, and one a case of sepsis with cloudy swelling of the liver. They offered no explanation of these readings.

Table 3 records the tests in which retention was noted in the thirty minute sample but none above 50 per cent in the five minute sample. It should be noted that only four tests (nos. 3, 10, 12 and 20) showed a five minute reading below 40, three of them being in cases of cirrhosis and the other probably having some injury of the liver. Only four of the twenty cases in this group had no definitely assigned hepatic or gallbladder disease. There is what may be considered a slight sluggishness of the liver in the removal of the bulk of the dye as shown by the first reading, and a definite lag in removal of the dye as shown by the thirty minute retention. This would appear to indicate definite but relatively slight impairment of hepatic function. Only five were below 40 years, and they had either hepatic or some other severe disease.

In table 4 eleven tests are listed in which there was greater than 50 per cent retention at five minutes but no dye remaining in the serum at thirty minutes. Three of these cases had no indications of hepatic or gallbladder disease, and these three cases gave only 52 per cent readings. In this group of cases there appears to be slight retardation in removal of the dye, but the removal is complete in thirty minutes.

TABLE 3.—*Tests Showing Retention at Thirty Minutes but Normal at Five Minutes*

No.	Age	Test No.	Rosenthal 5 Min.	Rosenthal 30 Min.	Van den Bergh Direct	Van den Bergh Indirect	Van den Bergh Quantitative	Comment
1	54	4	45	10	..	..	...	Chronic hepatitis
2	54	6	45	VFT*	..	..	...	Chronic cholecystitis
3	43	27	35†	10	..	..	...	Cirrhosis, hypertrophic, moderate
4	62	37	50	5	..	..	...	Cirrhosis, hypertrophic; arteriosclerosis
5	43	38	40	5	..	..	...	Cirrhosis, hypertrophic (first test 55 and 10)
6	65	42	48	5	..	..	..	Cirrhosis, hypertrophic and arteriosclerosis (see no. 9)
7	50	43	45	7	..	..	...	Syphilis, tertiary, of central nervous system (took 6 doses of arsphenamine after this test)‡
8	66	46	50	8	..	..	...	Cholecystitis, chronic; severe jaundice (3 months previous)
9	65	52	42	3	..	..	...	Same case as no. 6
10	40	66	38†	5	—	+ —	0.8	Cirrhosis, hypertrophic, early
11	25§	78	48	5	+	+	1.2	Hepatitis, acute (compare nos. 14 and 17)
12	35§	79	30†	FT*	—	+ —	0.8	Tonsillitis (possible hepatic hypertrophy)‡
13	50	86	40	10	—	++	1	Pernicious anemia (see no. 19)‡
14	25	92	45¶	3	+	+ —	1	Same case as no. 11
15	37§	95	45	5	..	..	...	Addison's disease; nephroptosis
16	37§	98	40	8	..	..	...	Hepatitis, acute (previous 100 and 38; 85 and 8; later 0 at 30 minutes)
17	25	100	45¶	3	—	+ —	0.8	Same case as no. 11 and 14
18	52	103	42	10	+ —	+	1	Cirrhosis, hypertrophic; adenomatous goiter and arteriosclerosis
19	50	110	40¶	3	..	..	...	Same case as no. 13
20	57	112	33†	3	..	..	...	Cirrhosis, hypertrophic, early; arteriosclerosis
21	60	114	50	6	..	..	...	Cirrhosis, hypertrophic, and arteriosclerosis
22	79	122	50	5	..	..	...	Cirrhosis (?); carcinoma of lung (?); senility
23	39§	126	50	12	..	..	...	Cirrhosis, severe; syphilis, tertiary; plastic
24	40	130	50	3	..	..	...	Cirrhosis, severe; syphilis, tertiary; plastic peritonitis, etc. (previous 48 and 0, 60 and 10, — and 8; Van den Bergh with first was ++, 1) (five doses of arsphenamine prior to second test)

* VFT means very faint trace; FT, faint trace.
† Indicates a five minute reading below 40.
‡ No hepatic disease assigned.
§ Under 40 years of age.
¶ Repeat tests.

TABLE 4.—*Cases with Retention Over Fifty at Five Minutes but Normal at Thirty Minutes*

No.	Age	Test No.	Rosenthal 5 Min.	Rosenthal 30 Min.	Comment
1	57	3	65	0	Van den Bergh, negative; acute cholecystitis
2	52	62	55	0	Van den Bergh, 0.8 units; chronic cholelithiasis, mild myocarditis
3	52	80	70	0	Early hypertrophic cirrhosis
4	54	82	52	0	Arteriosclerosis; senility; hernia
5	33	90	52	0	Observation of gastro-intestinal disease, not found; bad teeth
6	29	115	55	0	Van den Bergh, 1.3 units; cholangeitis, acute, catarrhal, moderately severe
7	50	120	52	0	Arteriosclerosis
8	63	123	60	0	Cirrhosis of liver (hypertrophic ?); arteriosclerosis; aortitis
9	45	124	60	0	Cholecystitis, chronic, moderate; cause undetermined (subicteric)
10	51	134	55	0	Colitis, chronic, atonic; arteriosclerosis
11	40	99	85	0	Van den Bergh, negative; syphilis, tertiary, of central nervous system (liver two fingerbreadths below costal border)

This would appear to indicate a degree of hepatic impairment less than in the foregoing group in table 3. There were only two below 40 years, and one of these had cholangeitis.

In table 5, the cases of cholecystitis, acute and chronic, and cholelithiasis are listed; three cases of cholangeitis are also shown. In considering these last cases, the question will arise as to whether or not they should be classed as hepatitis. The absence of any marked degree of hepatic tenderness or any appreciable degree of enlargement, and reliance on the clinician's differential ability have seemed to warrant

TABLE 5.—*Results in Cases of Disease of the Gallbladder and Bile Duct*

No.	Case No.	Age	Rosenthal 5 Min.	Rosenthal 30 Min.	Cholecystitis	Comment
1	3	57	65	0	Acute, catarrhal, moderate	Van den Bergh negative
2	28	51	85	5	Acute, (and arthritis, hypertrophic)	(Cirrhosis ?) third attack
3	18	25	35	0	Subacute, severe	Van den Bergh, — + — early + + +, 5.1 units)
4	6	54	45	VFT	Chronic (and arrested tuberculosis and myocarditis)	(Stones ?); operation stopped
5	21	33	45	0	Chronic (and appendicitis)	Van den Bergh, negative; (pathologic diagnosis: gallbladder normal; chronic obliterating appendicitis)
6	25	39	35	0	Chronic	Appendectomy, 1918
7	39	66	50	8	Chronic, with jaundice (stones ?)	Liver trouble since 1909; Van den Bergh, 14 and 9.2 units
8	90	45	60	0	Chronic	Pathologic diagnosis: thick wall with severe, chronic inflammation
9	94	53	50	0	Chronic (and arteriosclerosis, moderate, and arthritis)	Hypochlorhydria
10	19	40	35	0	Cholelithiasis	History of syphilis and intense treatment
11	51	52	55	0	Cholelithiasis (and myocarditis, mild)	Van den Bergh, negative; confirmed by operation
					Cholangeitis	
1	83	29	55	0	Acute, moderately severe	Drank much alcohol from 24 to 48 hours prior to attack; liver slightly enlarged, not tender
2	85	24	100+	100+	Acute, moderately severe	Liver at costal border; moderately tender
3	96	28	90	20	Acute, moderately severe	Liver barely palpable

their separate classification. All three patients were under 30. The second case gave a quantitative van den Bergh reaction of 20 units.

In the three cases of cholecystitis showing some thirty minute retention either hepatic involvement or a stone in the common duct was suspected. The limited number of cases would appear to bear out the observations of other students of this test, namely, that without obstruction of the hepatic bile flow or definite hepatic disease, disease of the gallbladder per se does not cause a retention.

In table 6 twenty-five cases of hepatic cirrhosis are listed, these being subgrouped as: atrophic, 1; unclassified, 5, and hypertrophic, 19. In the atrophic case the diagnosis was confirmed at autopsy. In only

eight of these was there more than 10 per cent retention at thirty minutes, and in but six of the remaining cases was there more than 5 per cent.

The average five minute reading in the thirty-two tests performed on this group was 61. Only seven cases showed a five minute retention of less than 50, and in two of these there was a higher reading at some other date. There appears, then, to be definite or potential hepatic insufficiency in the elimination of dye in this group, as evidenced by

TABLE 6.—*Hepatic Cirrhosis*

No.	Case No.	Age	Rosenthal 5 Min.	Rosenthal 30 Min.	Type	Comment
1	32	55	90	35	Atrophic	Autopsy confirmed; severe abscess of prostate
			90	38		
2	38	50	43	0	Unclassified	Endocarditis, slight (and nephritis ?)
3	53	40	38	5	Unclassified	Early; epigastric pain 9 years; ulcer treatment in 1922
4	61	52	70	0	Unclassified	Ulcer could not be confirmed
5	87	36	85	5	Unclassified	History of extensive antisyphilitic treatment in past
6	92	39	50	12	Unclassified	Moderately severe
7	5	39	55	15	Hypertrophic	Jaundice; gallbladder not visualized; tetrachlorphthalein tests positive
8	8	60	55	2	Hypertrophic	Arteriosclerosis; classified as severe
9	13	43	55	10	Hypertrophic	Moderate; possibly syphilitic
			40	5		
10	22	43	35	10	Hypertrophic	Classified as moderate
11	23	56	90	10	Hypertrophic	
12	31	62	50	5	Hypertrophic	Arteriosclerosis
13	35	65	48	5	Hypertrophic	Arteriosclerosis
			42	3		
14	37	40	48	0	Hypertrophic	Plastic peritonitis and syphilis, tertiary; (hepatitis ?); (classified as severe; treated with arsphenamine between first and second tests)
			60	12		
			—	8		
			50	3		
15	48	54	55	8	Hypertrophic	Anemia after lead poisoning; moderate cardiac hypertrophy
			88	23		
16	64	55	85	15	Hypertrophic	Arteriosclerosis, advanced; myocarditis; Van den Bergh negative
17	72	40+	90	10	Hypertrophic	Arteriosclerosis and tonsillitis; Van den Bergh, 1 and 1.7 units
18	75	52	42	10	Hypertrophic	Adenomatous goiter and arteriosclerosis; Van den Bergh, 1 unit
19	76	36	60	35	Hypertrophic	Syphilis, tertiary and syphilitic cirrhosis, severe (autopsied)
20	77	55	52	15	Hypertrophic	Pleurisy and hemorrhoids
21	78	60	95	8	Hypertrophic	Arteriosclerosis and hemorrhoids
22	79	55	60	2	Hypertrophic	Arteriosclerosis and senility, early
23	80	57	23	3	Hypertrophic	Arteriosclerosis
24	88	79	50	5	Hypertrophic	Carcinoma of lung; myocarditis; hydrothorax
25	89	63	60	0	Hypertrophic	Arteriosclerosis; hiccup; aortitis

but four cases giving no retention in thirty minutes, as well as by the higher average five minute retention. These are chronic cases, and the great reserve power of the liver as well as its ability to compensate by hypertrophy permits it to function relatively well even with considerable anatomic change. Yet some estimate as to the amount of impairment or degree of compensation may be judged by the retention of the dye, and a check on the hepatic function in cases of cirrhosis may aid in treatment, prognosis or contemplated surgical intervention.

There were three cases in which the diagnosis of syphilitic hepatitis was made or strongly favored, and seven cases apparently due to the

administration of arsphenamine. No. 6 (case 41, table 7) may be syphilitic instead of arsenical; the primary infection occurred in February, 1928. Only one of the arsenical cases was not also syphilitic. Six of the 100 per cent plus readings occurred in this series, all in severe cases and all showing a thirty minute retention above 45 (all but one above 70).

Ten other cases of syphilis occurring in this series are tabulated in table 8. In these cases a diagnosis of syphilis was made or a definite

TABLE 7.—*Hepatitis, Syphilitic and Arsenical*

No.	Case No.	Age	Rosenthal		Van den Bergh			Class	Comment
			5 Min.	30 Min.	Direct	Indirect	Quantitative		
1	7	65	100+ 85	45 18	3+ + —	3+ + —	8 0.9	Syphilitic	Syphilis, tertiary
2	46	50	35	0	2+	2+	4.4	Syphilitic	Jaundice cleared eight days previously
3	91	33	100+	85	...	...	...	Syphilitic	"Hepatitis, probably syphilitic"; syphilis
4	17	20	78 35	60 0	4+ 0	4+ + —	12 1	Arsenical	Under treatment; jaundice on reporting for next dose of arsphenamine; (second Van den Berg two weeks after second Rosenthal)
5	40	53	100+ 85 55 55 52 55	70 30 15 8 8 8	3+ 3+ 2+ + + — —	3+ 3+ 2+ + + — —	15.4 7.8 2.3 0.9 0.8 —	Arsenical	Dermatitis, severe; observation for acute yellow atrophy
6	41	21	100+	70	3+	3+	18.2	Arsenical	Jaundice seventeen days after fourth dose of arsphenamine; possibly syphilis
7	58	44	100+	95 10	3+ +	3+ +	15 1.6	Arsenical	Jaundice three days after second dose, second course; (second test seventeen days after first)
8	84	23	100+ 80	100 10	...	...	...	Arsenical	Jaundice and vomiting six to eight weeks after last dose of arsphenamine
9	93	24	60	8	...	...	...	Arsenical	Jaundice nine weeks after last dose of arsphenamine of second course
10	47	32	60	3	...	...	...	Arsenical	Not syphilitic; one dose of arsphenamine for pulmonary spirochetosis

history of previous diagnosis and treatment was obtained. Fifty per cent of these cases showed retention at thirty minutes, and all but one of these five cases had more than 50 per cent retention at five minutes. This case (case 36—no. 6, table 8) showed 45 per cent retention at five minutes and 7 per cent at thirty minutes, a definite indication of hepatic impairment. The patient was, therefore, not given arsenicals until prepared by a preliminary course of treatment, and consequently no acute hepatitis developed when neoarsphenamine was administered. It is believed that here the Rosenthal test was of definite preventive value. Only two cases gave less than 40 per cent five minute retention.

The three patients giving more than 40 per cent retention in five minutes and none in thirty minutes had received intensive antisyphilitic treatment during the past four to seven months with no evidence of hepatic embarrassment. However, these three patients received iodide and mercury preparation as a routine before the use of arsenicals.

TABLE 8.—*Other Syphilitic Cases in Series*

No.	Case No.	Age	Rosenthal 5 Min.	Rosenthal 30 Min.	Comment
1	1	51	45	0	Syphilis, tertiary, of central nervous system
2	2	36	45	0	Syphilis, tertiary, of central nervous system (? hepatic symptoms)
3	13	43	55	10	Hypertrophic cirrhosis; probably syphilis of central nervous system
			40	5	
4	19	40	35	0	Cholelithiasis; history of syphilis and treatment
5	30	52	25	0	Syphilis, tertiary, of central nervous system
6	36	50	45	7	Syphilis, tertiary; (took six doses of arsphenamine later following succinamide)
7	37	40	48	0	Syphilis, tertiary; hypertrophic cirrhosis; (? hepatitis); (received arsphenamine between first and second tests)
			60	12	
			50	8	
			50	3	
8	50	44	42	0	Syphilis, tertiary (gummatous change in lung)
9	76	36	60	35	Syphilis, tertiary, and syphilitic cirrhosis, severe; (autopsied)
10	87	36	85	5	Cirrhosis, unclassified; history of extensive antisyphilitic treatment in past

TABLE 9.—*Hepatitis, Nonsyphilitic and Nonarsenical*

No.	Case No.	Age	Rosenthal 5 Min.	Rosenthal 30 Min.	Van den Bergh Direct	Van den Bergh Indirect	Van den Bergh Quantitative	Diagnosis	Comment
1	4	54	45	10	...	...	...	Chronic hepatitis; arthritis	Wassermann reaction negative
2	15	38	40	0	...	...	...	Subacute; nephrolithiasis and peritonitis	No autopsy; Wassermann and Kahn reactions negative
			70	3					
3	45	30	100+	100	4+	4+	31.5	Acute hepatitis, severe, cause undetermined	Some tooth trouble
			72	4	2+	2+	4.6		
			80	4	2+	2+	3.5		
			100+	8	+	+	0.8		
			95	8	+	+	0.9		
4	52	25	70	5	+	+	2.4.	Acute (Van den Bergh 18 days before first Rosenthal 6.2 units)	Heavy drinking prior to attack
			48	5	+	+	1.2		
			45	3	+ —	+ —	1		
			45	3	—	+ —	...		
5	59	26	100	38	2+	2+	3.8	Acute hepatitis; (arsenical ?); (not syphilitic; Wassermann reaction negative)	Two doses of arsphenamine 10 days previously
			85	8	+	+ —	1		
			40	8	+ —	+ —	...		
			—	0	—	+ —	...		

The five patients with nonsyphilitic or nonarsenical hepatitis showed definite retention at some stage of the disease (table 9). None of the five minute readings were less than 40 per cent. One of these cases should probably be classed as arsenical (no. 5—case 59) as the patient admitted late in the illness that he "unofficially" received two injections of neoarsphenamine, but strongly denied syphilitic infection. No evidence of syphilis was found, and the Wassermann reaction of the blood was negative.

The seven cases of malignancy in which this test was applied showed a definite retention (table 10). All but two diagnoses were confirmed by operative or autopsy observations. Both of these showed definite hepatic enlargement. Several other writers have stressed the value of this test for determining hepatic metastases in cases showing no jaundice. As a guide to treatment, especially with regard to surgical intervention, the test is of much value.

Forty cases are listed in table 11 as clinically nonhepatic, that is, there was no clinical evidence to indicate hepatic involvement. In table 11 two cases (nos. 39 and 40, or cases 74 and 82) are included which were diagnosed hypertrophic cirrhosis. As noted, the diagnosis in these two cases was influenced by the Rosenthal test. Four other cases showed

TABLE 10.—*Malignancy*

No.	Case No.	Age	Rosenthal		Van den Bergh			Diagnosis	Comment
			5 Min.	30 Min.	Direct	Indirect	Quantitative		
1	26	62	60	22	2+	2+	8.3	Generalized abdominal carcinoma	Confirmed by operation; no autopsy
2	54	57	100+	70	3+	3+	17.1	Observation malignancy (pancreas ?)	Liver 1 inch above umbilicus
			100	58	3+	3+	16		
			100+	60	4+	4+	23.1		
3	55	53	100+	57	...	...	...	Carcinoma of liver, pancreas and stomach	Gastric distress for 20 years; no autopsy
4	56	46	80	35	2+	2+	8.9	Lymphosarcoma, retroperitoneal and mesenteric	Limited hepatic involvement but obstruction
5	68	42	100+	100	...	...	...	Generalized abdominal carcinoma	Confirmed by operation; no autopsy
6	81	37	100+	50	...	...	...	Melanosarcoma, generalized	Massive hepatic metastasis; autopsy
7	88	79	50	5	...	...	...	Carcinoma of lung (?); cirrhosis of liver (?)	Hydrothorax, right

more than a trace of retention at thirty minutes. No. 31 (case 9) probably had at least a congested liver. In no. 32 (case 36) the patient had syphilis, and it may be assumed that there was otherwise undiscovered hepatic injury. In no. 34 (case 65) the condition was diagnosed pernicious anemia, and the patient gave a history of dysentery in the Philippines in 1898, with a later history of watery stools with some blood for the past few years. One month prior to admission he had been jaundiced. In this case there were two possibilities: either that he had injury to the liver from intestinal infection and toxemia, or that there was some change in hepatic function in such a severe disease of the blood as pernicious anemia. No. 36 (case 71) cannot be explained; there is some question as to whether this is actually a case of Addison's disease.

The average five minute reading for this entire group was 42.07 per cent. If the seven readings in the six cases which also showed more than a trace of dye in thirty minutes are omitted, the average five

minute reading for the remaining thirty-four cases becomes 39.85 per cent—approximately 40 per cent.

If these thirty-four cases are subdivided into two groups, one to include all cases with a five minute retention greater than 40 per cent

TABLE 11.—*Nonhepatic Cases*

No.	Case No.	Age	Rosenthal 5 min.	Rosenthal 30 Min.	Diagnosis	Comment
1	1	51	45	0	Syphilis, tertiary, of central nervous system	
2	2	36	45	0	Syphilis, tertiary, of central nervous system	(? of hepatic symptoms)
3	10	41	35	0	Constipation, chronic, severe	
4	11	63	38	0	Arteriosclerosis, myocarditis	
5	12	54	35	0	Diabetes mellitus, severe	
6	14	60	50	0	Arteriosclerosis	
7	16	55	50	0	Multiple neuritis, sequelae	
8	20	38	45	0	Spastic colitis	
9	27	29	30	0	Chronic nephritis	
10	29	50	22	0	Myocarditis and hypertension	
11	30	52	25	0	Syphilis, tertiary, of central nervous system	
12	33	31	25	0	Appendicitis, chronic	Pathologic diagnosis: acute exacerbation
13	34	?	42	0	Enterocolitis, chronic, recurrent	
14	42	38	25	0	Varicose veins and ureteral kink	Cholecystectomy, 1925
15	43	15	20	0	Stomatitis	Slight gastric symptoms
16	44	34	30	0	Gastritis, chronic	Probably alcoholic
17	49	39	50	0	Gastritis, chronic	
18	50	44	42	0	Syphilis, tertiary	Pulmonary gumma
19	57	47	50	0	Duodenal ulcer and chronic appendicitis	Confirmed by operation
20	62	34	32	0	Neurasthenia	
21	66	30	20	0	Gastric neurosis and tonsillitis	
22	67	33	52	0	Observation, gastro-intestinal disease not found	Bad teeth
23	69	42	38	0	Myelogenous leukemia	
24	86	50	52	0	Arteriosclerosis	
25	95	40	45	0	Arteriosclerosis, constipation	
26	98	36	45	0	Alcoholism, chronic, severe	
27	99	56	40	0	Duodenal ulcer, chronic	
28	63	54	52	0	Arteriosclerosis, senility, hernia	
29	97	51	55	0	Colitis, chronic, atonic and arteriosclerosis	
30	100	46	45	0	Arteriosclerosis, eczema	Disease of gallbladder not found
31	9	35	90	15	Valvular heart disease; (mitral regurgitation and stenosis; auricular fibrillation)	Probable congested liver
32	36	50	45	7	Syphilis, tertiary, of central nervous system	Took six shots of arsphenamine later, following succinamide
33	60	35	30	FT	Tonsillitis	"Possible hepatic hypertrophy"
34	65	50	40 40	10 3	Pernicious anemia	Jaundice; history of dysentery, 1898
35	70	78	52	Trace	Cardiac hypertrophy and arteriosclerosis	Congestion ?
36	71	37	45	5	Addison's disease and nephroptosis	
37	73	40	85	0	Syphilis, tertiary, of central nervous system	
38	21	47	38	0	Arteriosclerosis, general, moderate	
39	74	47	60	3	Hypertrophic cirrhosis; arteriosclerosis; myocarditis	Diagnosis influenced by Rosenthal test
40	82	47	50	6	Hypertrophic cirrhosis; arteriosclerosis	Diagnosis influenced by Rosenthal test; liver not enlarged

which have a diagnosis warranting a suggestion of hepatic involvement, and the other group including the remainder, rather interesting and perhaps instructive figures are obtained.

In table 12 are tabulated the first subgroup of nonhepatic cases. The diagnoses in these cases are considered sufficient to warrant at

least a suggestion of hepatic involvement. The average five minute retention of this group was 49.4 per cent.

In the second subgroup of nonhepatic cases, all but two of the five minute readings were below 40 per cent (table 13). The diagnoses,

TABLE 12.—*Nonhepatic Cases with More than 40 Per Cent Five Minute Retention (with Diagnosis Permitting Suggestion of Hepatic Involvement)* *

No.	Case No.	Rosenthal 5 Min.	Rosenthal 30 Min.	Diagnosis
1	1	45	0	Syphilis, tertiary, of central nervous system
2	2	45	0	Syphilis, tertiary, of central nervous system
6	14	50	0	Arteriosclerosis
8	20	45	0	Spastic colitis
13	34	42	0	Enterocolitis, chronic, recurrent
17	49	50	0	Gastritis, chronic
18	50	42	0	Syphilis, tertiary
19	57	50	0	Duodenal ulcer and chronic appendicitis
24	86	52	0	Arteriosclerosis
25	95	45	0	Arteriosclerosis, constipation
26	98	45	0	Alcoholism, chronic, severe
27	99	40	0	Duodenal ulcer, chronic
28	63	52	0	Arteriosclerosis; senility; hernia
29	97	55	0	Colitis, chronic, atonic and arteriosclerosis
30	100	45	0	Arteriosclerosis; eczema (disease of gallbladder not found)
35	70	52	Trace	Cardiac hypertrophy and arteriosclerosis
37	73	85	0	Syphilis, tertiary, of central nervous system
Totals	17	840		
Average		49.4		

* Of the cases listed in table 11, nos. 5, 31, 32, 34, 36, 39 and 40 are omitted as cases with probable hepatic involvement.

TABLE 13.—*Nonhepatic Cases with Less than 40 Per Cent Five Minute Retention (Except for Two Above Fifty Who Showed no Condition Permitting Suggestion of Hepatic Involvement)*

No.	Case No.	Rosenthal 5 Min.	Rosenthal 30 Min.	Diagnosis
3	10	35	0	Constipation, chronic, severe
4	11	38	0	Arteriosclerosis; myocarditis
5	12	35	0	Diabetes mellitus, severe
7	16	50	0	Multiple sclerosis, sequelae of
9	27	30	0	Chronic nephritis
10	29	22	0	Myocarditis and hypertension
11	30	25	0	Syphilis, tertiary, of central nervous system
12	33	25	0	Appendicitis, chronic
14	42	25	0	Varicose veins and ureteral kink (cholecystectomy, 1925)
15	43	20	0	Stomatitis
16	44	30	0	Gastritis, chronic (probably alcoholic)
20	62	32	0	Neurasthenia
21	66	20	0	Gastric neurosis and tonsillitis
22	67	52	0	Observation; gastro-intestinal disease not found (bad teeth)
23	69	38	0	Myelogenous leukemia
33	60	30	FT	Tonsillitis; "possible hepatic hypertrophy"
38	21	38	0	Arteriosclerosis, general, moderate
Totals	17	545		
Average		32		

histories and physical observations in these two cases were not considered definite enough to permit placing them in table 12. The average five minute retention of this group of seventeen cases was 32 per cent.

In these last two tables a feature is demonstrated which had repeatedly impressed me while studying the series of cases, namely, that a five

minute retention between 40 and 50 per cent should create a suggestion of hepatic involvement. As these five minute retentions above 40 per cent occur frequently in cases showing no retention at the thirty minute period, it is my belief that the five minute sample should always be obtained, if possible.

SUMMARY

1. One hundred and thirty Rosenthal bromsulphalein tests in 100 cases are reported. No unfavorable reactions or results have been observed.

2. Thirty-seven tests showed no retention above Rosenthal's normal figures. The average five minute reading for this group was 38 per cent.

3. Fifty-five tests showed a retention above normal in both samples.

4. Fourteen five minute samples are recorded above 100 per cent. This is unexplained, but bilirubinemia seems to be a causative factor.

5. Of twenty-four tests showing a thirty minute retention and 50 per cent or less at five minutes, only four fell below 40 per cent at five minutes.

6. Eleven cases showed greater than 50 per cent at five minutes and no retention at thirty minutes. All but three had some hepatic or gallbladder disease.

7. Cases of disease of the gallbladder and bile duct gave no retention except when there was hepatic involvement, definite or suspected.

8. Of twenty-five cases of hepatic cirrhosis, 44 per cent (eleven cases) showed 5 per cent or less retention at thirty minutes; the average five minute reading of this group (thirty-two tests) was 61 per cent. Only five cases showed less than 50 per cent retention at five minutes (two others did but had other higher retentions). Only four cases showed no thirty minute retention.

9. All of the seven cases of arsenical hepatitis showed retention. Two of three cases of syphilitic hepatitis showed retention; the third case had been free from jaundice for eight days preceding the Rosenthal test. One case of the arsenical group showed permanent injury by the Rosenthal test after the van den Bergh reaction had become negative.

10. Five of ten other patients in the series who had syphilis, but no diagnosis of hepatic involvement, showed retention. In cases of syphilis with suspected hepatic involvement the control of arsenical treatment by this test is indicated.

11. All but one of fifteen cases of hepatitis showed definite retention. The one exception was not tested until eight days after jaundice had disappeared (tables 7 and 9).

12. The observations of others in malignant disease of the liver are confirmed.

13. Forty cases (40 per cent of the series) were not considered clinically as evidencing hepatic involvement. Two of these were diagnosed cirrhosis of the liver, but the diagnosis was influenced by the Rosenthal test. In three of the four other cases showing more than a trace of dye retention at thirty minutes hepatic dysfunction could reasonably be assumed. Omitting these six cases, the average for the remainder of the group was 40 per cent retention at five minutes.

CONCLUSIONS

1. The bromsulphalein dye, used as directed by Rosenthal, is of distinct value in determining the presence and degree of hepatic dysfunction.

2. Bromsulphalein is safer, less toxic, less irritating and easier to use than phenoltetrachlorphthalein.

3. From 35 to 38 per cent may be considered as the normal average five minute retention.

4. Between 40 and 50 per cent retention at five minutes should create suspicion of hepatic disorder. Other criteria need to be used in such a case.

5. Above 50 per cent retention at five minutes is strongly suggestive of hepatic disease or disorder, and combined with a thirty minute retention is almost diagnostic of injury to the liver.

6. The test is of special value (1) in determining functional or anatomic damage to the liver in cases of disease of the gallbladder or bile duct, (2) in determining hepatic involvement in cases of malignancy, (3) in controlling antisyphilitic arsenical treatment, (4) in determining the degree of residual disorder after acute disease of the liver, (5) in determining hepatic involvement in cases of tertiary syphilis and (6) in confirming suspected disease of the liver without jaundice.

7. The five minute sample is of such frequent value that it should be collected as a routine.

8. This test is a valuable addition to the means of study of hepatic disease, but it should not be allowed to replace thorough clinical observation nor should it be used independently of other tests if they are indicated.

CALCIUM STUDIES

VI. THE EFFECT OF PARATHYROID EXTRACT ON THE DIFFUSIBILITY OF CALCIUM IN HUMAN BEINGS *

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A decreased total serum calcium is a constant observation in parathyroprivic tetany, but there is considerable difference of opinion in the literature as to the distribution of the diffusible and nondiffusible fractions in this condition. The divergent results obtained may be explained in part by the fact that different experimental methods have been used by different investigators. For reasons which have been stated previously [1] it seems that, from a physiologic point of view, the consideration of the cerebrospinal fluid as the diffusible portion of the serum calcium is more satisfactory than the determination of diffusible calcium by ultrafiltration or dialysis.

Cameron and Moorhouse [2] found that in parathyroidectomized dogs the total serum calcium was greatly diminished but that the spinal fluid calcium was little altered. They concluded that in parathyroprivic tetany the reduction is in the nondiffusible calcium. The same conclusion was reached by Cruickshank.[3] On the other hand, Moritz [4] and von Meysenbug and McCann [5] noted a reduction in both diffusible and nondiffusible calcium in the same ratio. Moritz [6] found that following the injection of parathyroid extract in rabbits, there was an increase in both diffusible and nondiffusible calcium, the increase being more marked

* Submitted for publication, June 15, 1929.

* From the Medical Service of Dr. Thomas McCrae and the Department for Diseases of the Chest, Jefferson Hospital.

1. Cantarow, A.: Calcium Studies: V. The Relationship Between the Calcium Content of Cerebrospinal Fluid and Blood Serum in Health and in Disease, Arch. Int. Med. **44**:670 (Nov.) 1929.

2. Cameron, A. T., and Moorhouse, V. H. K.: Tetany of Parathyroid Deficiency and the Calcium of the Blood and Cerebrospinal Fluid, J. Biol. Chem. **63**:687, 1925.

3. Cruickshank, E. W. H.: Studies on Experimental Tetany, Biochem. J. **17**:13, 1923.

4. Moritz, A. R.: The Effect of Ultra-Violet Radiation on the State of Serum Calcium, J. Biol. Chem. **64**:81, 1925.

5. Von Meysenbug, L., and McCann, G. F.: The Diffusible Calcium of the Blood Serum: 2. Human Rickets and Experimental Tetany, J. Biol. Chem. **47**:541, 1921.

6. Moritz, A. R.: The State of the Serum Calcium in Experimental Hypo- and Hyper-Calcemia, J. Biol. Chem. **66**:343, 1925.

in the diffusible fraction. Liu [7] injected parathyroid extract into two patients with parathyroid tetany and found that the total serum calcium rose, the rise being greater in the diffusible than in the nondiffusible portion.

In the present investigation simultaneous determinations of the blood serum and cerebrospinal fluid calcium in eleven patients were made, before and at four hour intervals after the intramuscular injection of 40 units of parathyroid extract.[8] The patients included four with essential epilepsy, two with mental deficiency, two imbeciles and three with bronchial asthma. The location of the patients necessitated the lapse of thirty-six hours between the collection of the material and the calcium determinations. Numerous checks on serum and spinal fluid, which was allowed to stand at room temperature for forty-eight hours, showed no change in calcium content beyond the experimental

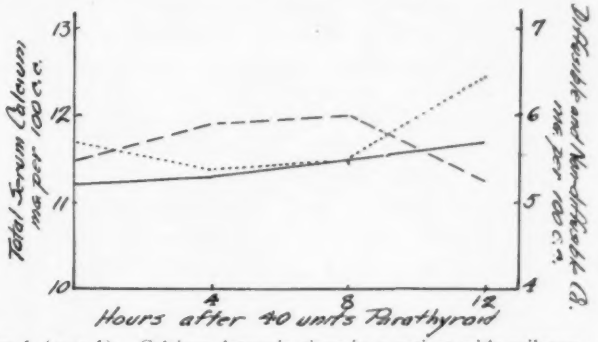

Chart 1 (case 1).—Calcium determinations in a patient with epilepsy. In this and the following charts, the relationship between the total blood serum calcium and its diffusible and nondiffusible fractions before and at four hour intervals after the intramuscular administration of 40 units of parathyroid extract are shown. The total calcium is represented by the solid line, the diffusible calcium by the broken line and the nondiffusible calcium by the dotted line.

error of 2 per cent. The method used for the calcium determinations was the Clark-Collip modification of the Kramer-Tisdall method for determining serum calcium.[9]

7. Liu, S. H.: The Partition of Serum Calcium into Diffusible and Nondiffusible Portions, Chinese J. Physiol. **1**:331, 1927.

8. The preparation used was parathyroid extract-Collip, supplied by Eli Lilly and Company, through the courtesy of Dr. J. H. Warvel.

9. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Calcium with a Suggested Modification, J. Biol. Chem. **63**:461, 1925.

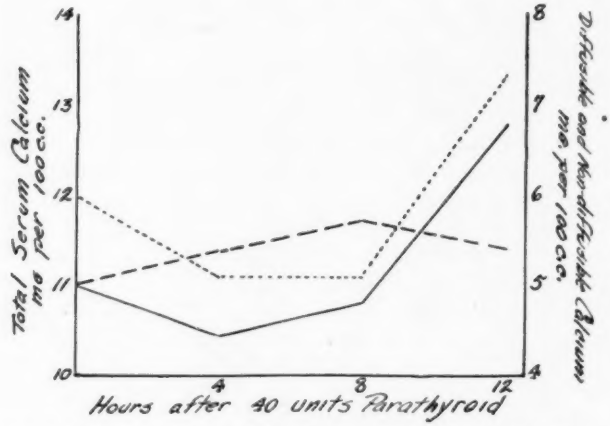

Chart 2 (case 2).—Calcium determinations in a patient with epilepsy.

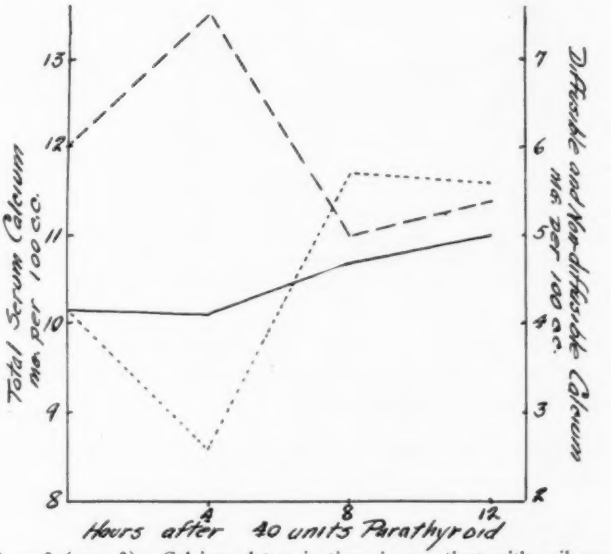

Chart 3 (case 3).—Calcium determinations in a patient with epilepsy.

EXPERIMENTAL DATA

The results obtained are shown in the accompanying charts. The term "diffusible" is applied to the cerebrospinal fluid calcium, the difference between it and the total serum calcium being considered nondiffusible.

Total Serum Calcium.—The serum calcium before the injection of parathyroid extract was from 7 to 11.5 mg. per hundred cubic centimeters, the figures for the three patients with asthma being 7, 7.5 and 8.5 mg. One patient with epilepsy had a serum calcium of 11.2 mg., and one with imbecility, 11.5 mg.; the other figures were within the normal limits of from 9 to 11 mg. As was noted in previous studies,[10] there was a general tendency toward an increase in serum calcium, the most marked rise occurring from eight to twelve hours after the injection in most instances. In cases 1, 3 and 5, the increase was comparatively slight. However, as Hunter and Aub[11] have pointed out, alterations in calcium metabolism may follow the administration of the parathyroid hormone without any significant change in the level of serum calcium. In the patients with bronchial asthma a marked elevation occurred, amounting to 5.2 mg. in case 2.

Cerebrospinal Fluid Calcium.—The control values ranged from 4.9 to 6 mg. The normal cerebrospinal fluid calcium was found in a previous study[1] to be from 4.5 to 5.5 mg. per hundred cubic centimeters. In this group of patients five showed figures above normal: case 3, epilepsy, 6 mg.; case 5, imbecility, 5.8 mg.; case 8, mental deficiency, 5.6 mg.; cases 10 and 11, bronchial asthma, 6 mg. and 5.7 mg., respectively. Following the injection of parathyroid extract, the general trend was toward a rise in the spinal fluid calcium. In only two instances (cases 6 and 7) did this figure fail to rise above the high limit of normal. In only two patients, however, was the elevation marked (cases 3 and 5), and it appears significant that in case 3 an increase of 1.5 mg. at the end of four hours was accompanied by a slight decrease in the total serum calcium. Another observation worthy of attention is that in two of the patients with bronchial asthma (cases 10 and 11) there was a preliminary fall in cerebrospinal fluid calcium at the end of four hours, coincident with a definite rise in total serum calcium.

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10. Cantarow, A.; Caven, W. R., and Gordon, B. L.: Changes in the Chemical and Physical Characteristics of the Blood Following the Administration of Parathyroid Hormone, Arch. Int. Med. **38**:509 (Oct.) 1926. Cantarow, A.; Dodek, S. M., and Gordon, B. L.: Calcium Studies in Jaundice, Arch. Int. Med. **40**:129 (Aug.) 1927.

11. Hunter, D., and Aub, J. C.: Lead Studies: 15. The Effect of Parathyroid Hormone upon the Excretion of Lead and of Calcium in Patients Suffering from Lead Poisoning, Quart. J. Med. **20**:136, 1927.

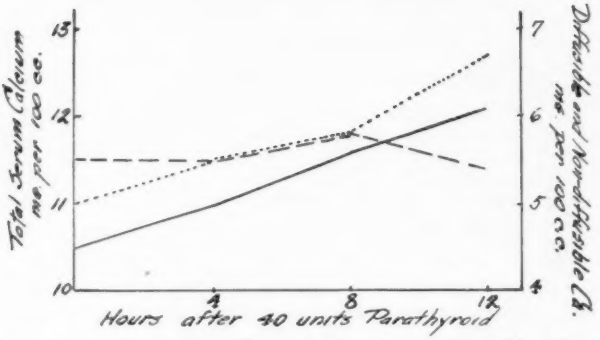

Chart 4 (case 4).—Calcium Determinations in a patient with epilepsy

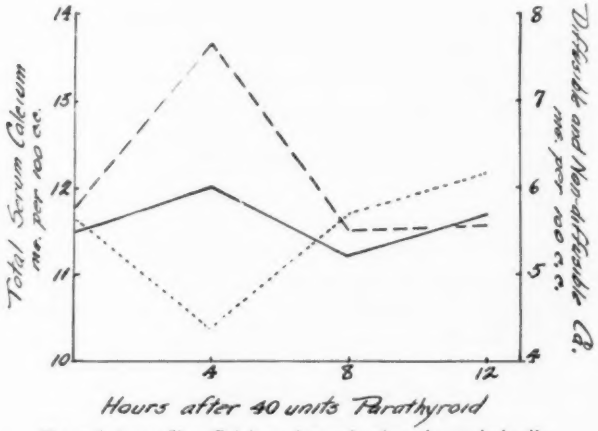

Chart 5 (case 5).—Calcium determinations in an imbecile.

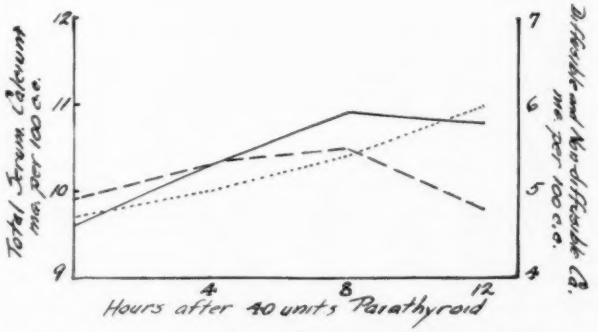

Chart 6 (case 6).—Calcium determinations in an imbecile.

Nondiffusible Calcium.—The normal values for nondiffusible calcium in a previous series were from 4.7 to 5.75 mg. per hundred cubic centimeters.[1] In the present series five were within normal limits, one (case 2, epilepsy) was above normal (6 mg.), and five were below normal (case 3, epilepsy, 4.15 mg.; case 7, mental deficiency, 3.95 mg.; cases 9, 10 and 11, bronchial asthma, 1.8, 1.5, 2.8 mg., respectively).

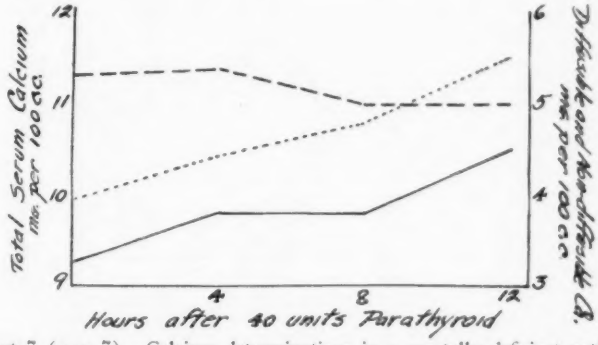

Chart 7 (case 7).—Calcium determinations in a mentally deficient patient.

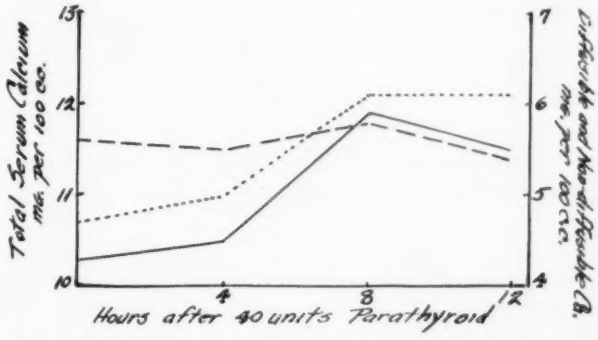

Chart 8 (case 8).—Calcium determinations in a mentally deficient patient.

After the injection of parathyroid extract, there was a distinct elevation of nondiffusible calcium in every case. The greatest rise was found at the end of the twelve hour period in all but one patient (case 10). This patient was the only one in whom the nondiffusible calcium did not exceed the diffusible at the end of twelve hours, although prior to the injection the reverse was the case in all but two instances (cases 1 and 2).

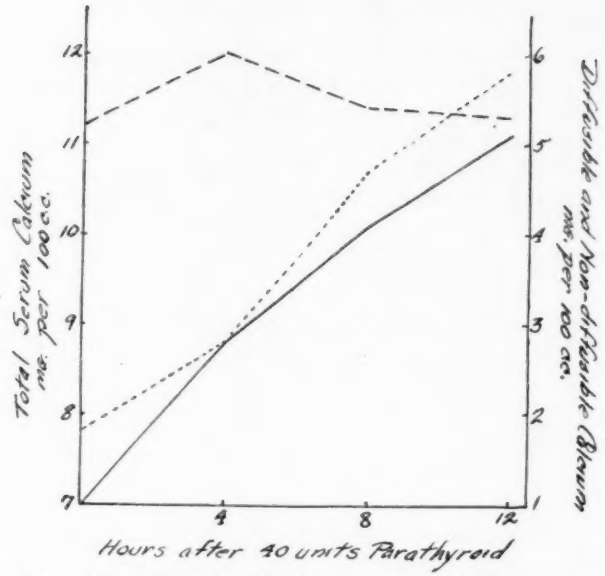

Chart 9 (case 9).—Calcium determinations in a patient with bronchial asthma.

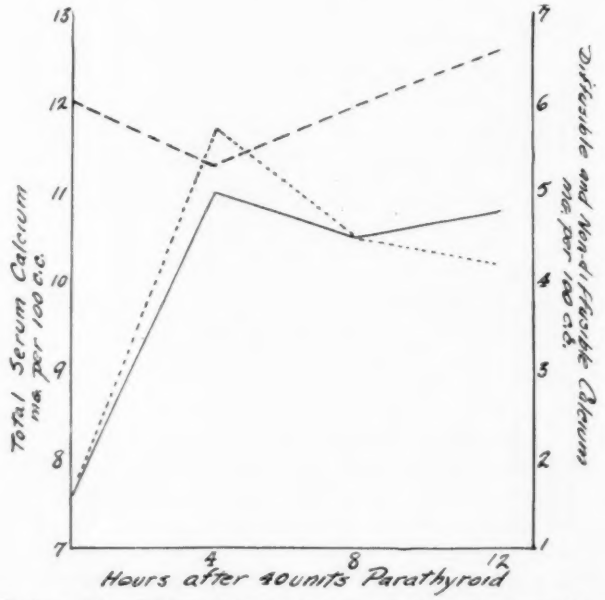

Chart 10 (case 10).—Calcium determinations in a patient with bronchial asthma.

Ratio of Diffusible to Nondiffusible Calcium.—The change that follows the administration of parathyroid extract may be shown by a consideration of the ratio of diffusible to nondiffusible calcium as illustrated in the accompanying table. In five cases there was an increase in the ratio at the end of four hours, but at the end of the twelve hour period the figure was below the control in every patient, the lowest figure in every case but one (case 10) being obtained at this time.

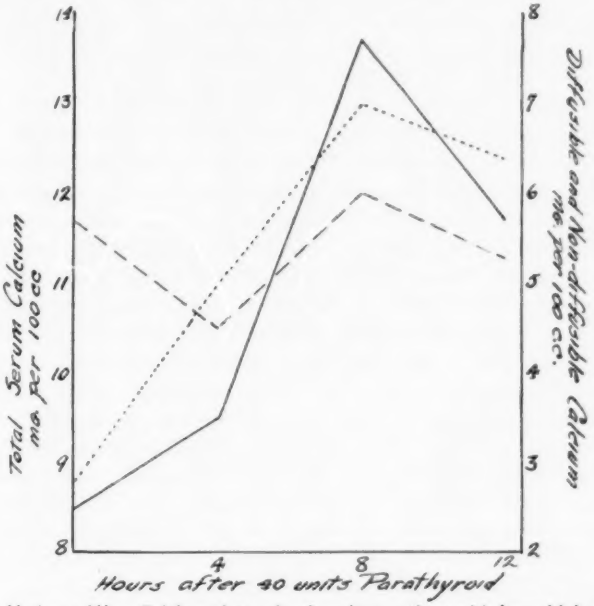

Chart 11 (case 11).—Calcium determinations in a patient with bronchial asthma.

The Ratio of Diffusible to Nondiffusible Calcium Before and at Four Hour Intervals After the Intramuscular Injection of 40 Units of Parathyroid Extract

Cases	Control*	4 Hours*	8 Hours*	12 Hours*
1	98	109	109	81
2	88	105	111	73
3	144	286	87	96
4	110	109	100	81
5	101	175	93	91
6	104	106	101	80
7	134	120	104	91
8	119	110	95	88
9	288	214	115	91
10	400	93	133	157
11	203	90	86	82

* Ratios expressed as percentages.

COMMENT

Parathyroid extract appears to affect both the diffusible and the nondiffusible fractions of serum calcium. In this respect, the observations in the present study confirm those of Moritz.[6] He believed, however, that the diffusible calcium was affected more than the nondiffusible, whereas the figures in the present study seem to indicate that the reverse is the case. This apparent contradiction may be due, as previously suggested, to the difference in experimental method. Furthermore, the work of Moritz was done on rabbits, a species which appears to be much less responsive to parathyroid extract than other animals. It would seem that a more exact index of the calcium distribution in the tissues is obtained by the simultaneous determination of blood serum and cerebrospinal fluid calcium, which takes into account the variable factor of cell membrane permeability. This factor is disregarded in dialysis and ultrafiltration experiments, a fact which may be of particular importance in view of the decided effect of calcium on cell permeability.

The most marked increase in nondiffusible calcium occurred in patients in whom this factor was originally low, as in those with bronchial asthma. That the diffusible and nondiffusible values may vary independently is evidenced by the fact that at times both increased simultaneously (cases 6, 9 and 11), and at times an increase in one was accompanied by a decrease in the other. That the level of diffusible calcium is not entirely dependent on the total serum calcium is shown in cases 2, 3 and 10, in which the former factor increased coincidently with a diminution in the latter. The same point is illustrated strikingly in cases 9, 10 and 11, and to a lesser degree in other instances, in which the reverse condition prevailed; namely, a decrease in diffusible calcium coincidently with an increase in total serum calcium.

It appears, therefore, that the parathyroid hormone, in some cases showing a normal calcium distribution, causes a preliminary increase in the ratio of diffusible to nondiffusible calcium, followed by a more marked and more prolonged decrease in this ratio. In other instances, particularly those with a low nondiffusible fraction, the ratio decreases steadily over the twelve hour period. Variations in this ratio bear no constant relation to the total serum calcium.

THE SYSTOLIC BLOOD PRESSURE IN DUODENAL AND IN GASTRIC ULCER

A STATISTICAL STUDY *

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AND
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WITH THE TECHNICAL ASSISTANCE OF LYDIA PETRICH
ROCHESTER, MINN.

This study was undertaken with the hope of determining whether or not patients suffering from duodenal or gastric ulcer have low systolic blood pressures. The data were compiled from the records of patients with duodenal or gastric ulcer examined in the Mayo Clinic by a diversified but well trained group of internists. Thus, multiple personal equations are expressed in the readings of blood pressure. No reading was taken with the subject under consideration in mind. The readings were impersonally recorded, by the auscultatory method, usually with the patient in the sitting position, using a spring sphygmomanometer. These instruments are corrected for variations against a mercury sphygmomanometer every seven days, so that it would be impossible to have a gross mechanical error in reading. The readings were recorded immediately on a history sheet, and from these records the charts were compiled and curves constructed. This work was done by a statistician who had no knowledge of the preconceived hypothesis. The compilation and mathematics of biometry were checked throughout by other statisticians. We are therefore able to transcribe the results in charts, curves and explanations for a matter of record.

The first series of cases studied comprised 865 of duodenal ulcer and 561 of gastric ulcer. In selecting the patients, the question of whether blood pressure was normal or abnormal was not considered. The series included cases of severe hypertension, due to independent conditions associated only by coincidence.

The data were corrected for age and weight against 1,016 cases encountered in the routine of work at the clinic, in some of which the general examination gave negative results; cases of ulcer and of carcinoma of the stomach were excluded from this group. The patients in this group, which was used as a control, were not all normal, but cases of hypotension as well as of hypertension were included and the weight distribution (thin, normal and stout) seemed fairly regular.

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* From the Division of Medicine, the Mayo Clinic.

In making the corrections for age and weight the cases were divided into age groups, and each group was subdivided, according to weight, into three classes called, respectively, "thin," "normal" and "stout." In making up the classes according to weight, consideration was given to age and height as well as to weight. A chart of normal weight was employed as a standard in this part of the work of classification. In order to obtain a so-called normal group, cases were considered to be normal in which the data were 5 per cent above or 5 per cent below the normal as established on the standard chart. The control cases were similarly grouped and classified. In the control cases, the mean blood pressures were calculated for the patients in each of the three weight groups. Then the results in the various age groups and weight classes in the cases of ulcer were corrected against the values established for the groups and classes in the control group. As shown in the following problem, the mean blood pressure (n, o or p) was calculated in each age group and in each of the three weight classes. The result, in each instance, was multiplied by the frequency (a, b or c, that is, the number of patients in the group) in the corresponding weight class of the group of patients with ulcer. The sum of these products was divided by the sum of the frequencies in the group with ulcer (d), and the quotient was an average (r) which represented the mean blood pressure in the control cases if they had been distributed as the cases of ulcer were distributed, according to weight. Then the mean blood pressure for persons of all builds in the control group (s) was divided by the average (r). The quotient represented the correction for weight (z). The figure represented by z usually fell close to 1. If, in the cases for which correction was being made, there was a tendency to obesity, z would be less than 1, for example, 0.997. If, however, the tendency was to emaciation, z would be greater than 1, for example, 1.004. This calculation also made correction for age at the same time, since each result involved all cases in a certain age group. Throughout the study, the various age groups were made up of persons who fell within the same upper and lower limits according to age. The following example shows the correction of data for age and weight:

		Disease Group, Frequency		Control Group, Blood Pressure Means
Age Group, Years 25-29	Thin	a	$\times$	$n = an$
	Normal	b	$\times$	$o = bo$
	Stout	c	$\times$	$p = cp$
		d		m

$m + d = r$; $s \div r = z$ ($s =$ mean of control cases, all builds; z is the "weight correction").

$z \times$ mean of group being corrected = "corrected mean."

In order to make the comparison fairer, three additional groups were studied. One of these comprised 1,685 cases of cholecystitis. In 782 cases in this group, cholelithiasis was present. The data were corrected for age and weight against the control group, and were compared with those in the cases of ulcer. Since the data in the ulcer group and in the group of cases of disease of the gallbladder were corrected with those of the same control group, it is not significant whether or not the control group was normal.

The second of the three additional groups to undergo analysis was made up of 571 cases of inoperable carcinoma of the stomach and 239 cases of carcinomatous gastric ulcers; the data were corrected for age and weight. The cases of inoperable carcinoma selected because of the patients' low systemic resistance had all been proved by the surgeon to be inoperable.

The third of the three additional groups was made up of cases the reports of which were obtained from one life insurance company.[1] We did not use the "normal blood pressure curve" that was used by the company, but derived averages, by calculation, from the frequency distribution of the various blood pressures in five-year age groups of

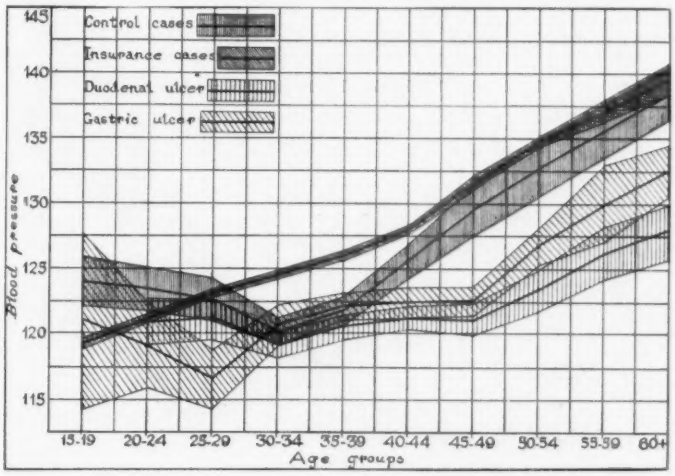

Chart 1.—Systolic blood pressure in cases of duodenal and gastric ulcers compared with blood pressure in control cases and life insurance cases (males).

all persons who applied for life insurance during a given period. This group contained 4,209 men and 1,518 women, and included some persons who had been rejected and others with abnormal blood pressure. The averages that were derived correspond fairly well with other averages obtained from life insurance tables [2] and from army statistics,[3]

1. Furnished by W. G. Exton, director of laboratories and longevity service, Prudential Life Insurance Company of America.

2. Hunter, Arthur; and Rogers, O. H.: Blood Pressure as Affected by Sex, Weight, Climate, Altitude, Latitude or by Abstinence from Alcoholic Beverages, Assn. Life Insur. Med. Directors of America **6**:92, 1919-1920.

3. Fleming, W. D.: Blood Chemistry and Blood Pressure Standards: I. The Effect of Tropical Residence on the Blood Chemistry and the Blood Pressure, J. Metab. Research **6**:87, 1924.

except that the derived averages were a little higher in the later years of life, especially in women. Nevertheless, the derived average seems to give a fair "average blood pressure." Whether or not the derived average can be called normal is a question. We were unable to correct this group for weight because the height and weight were not available in each case in the series.

All material was divided according to sex, and arranged in five-year age groups. The mean blood pressures with their probable errors and

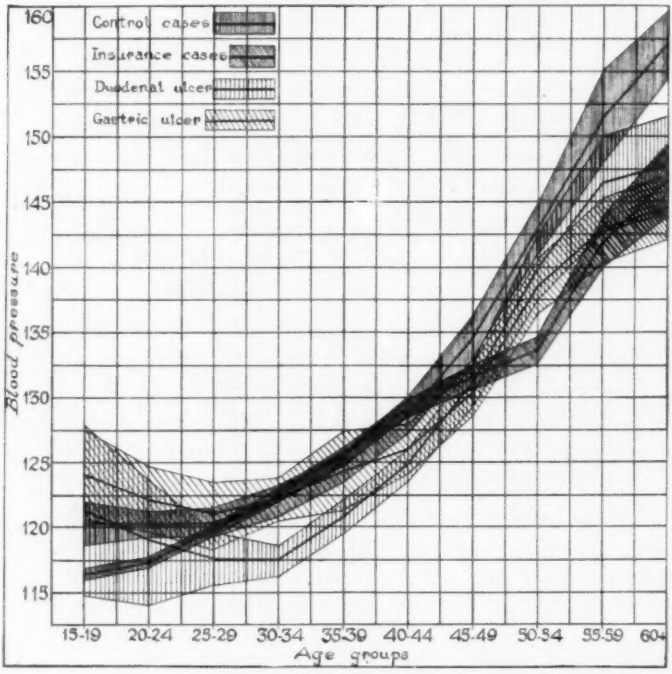

Chart 2.—Systolic blood pressure in cases of duodenal and gastric ulcers compared with blood pressure in control cases and life insurance cases (females).

standard deviations were calculated for all of the age groups. All of the curves were smoothed, and the probable errors are shown in charts 1, 2, 4, 5, 6 and 7. The plus and the minus errors are shown, respectively, by the shaded areas above and below the middle line which represents the actual mean.

4. Rugg, H. O.: Statistical Methods Applied to Education, Boston, Houghton Mifflin Company, 1917, pp. 97 and 184.

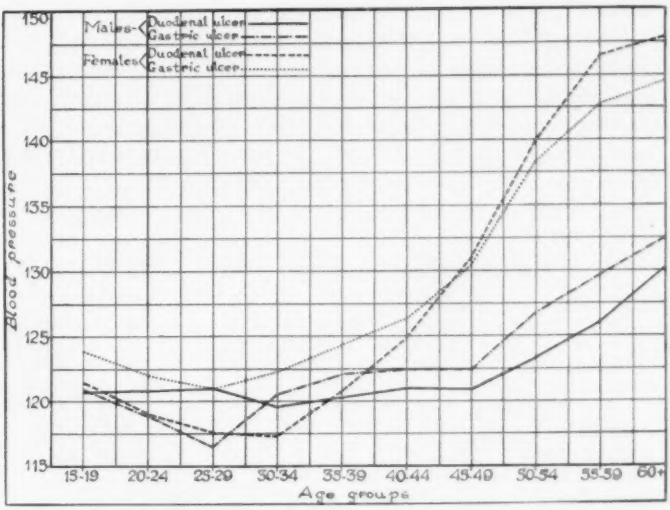

Chart 3.—Systolic blood pressure in cases of gastric and doudenal ulcers (males and females).

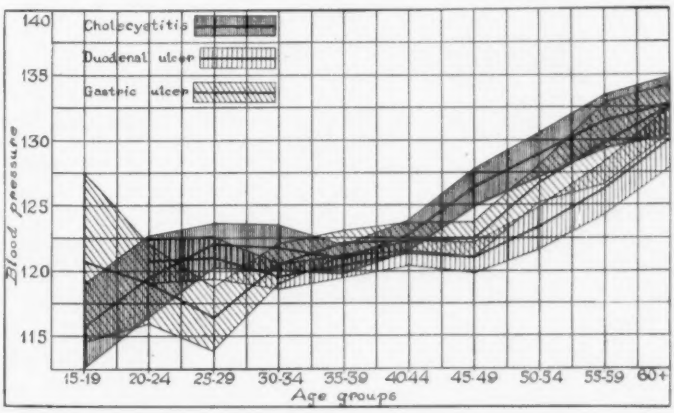

Chart 4.—Systolic blood pressure in cases of duodenal and gastric ulcers compared with blood pressure in cases of cholecystitis (males).

In chart 1, constructed from statistics derived from male patients, the difference between the curve of blood pressure, as derived from the insurance figures, and that in cases of duodenal ulcer, varies from 0.3 to 11.4 mm.; in the cases of duodenal ulcer the systolic blood pressure falls below that of the insurance cases. From the ages of 30 to 59, the difference between the mean blood pressure in the insurance group and the corrected mean in the duodenal ulcer group, divided by its probable error, is 4.9 or more, with 1,052 or more chances to 1 that the difference is significant.[5] The blood pressures in the cases of gastric ulcer in

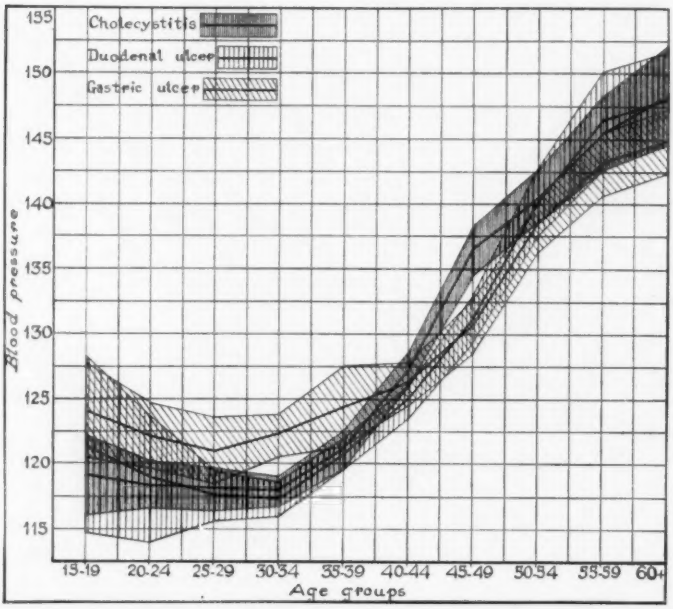

Chart 5.—Systolic blood pressure in cases of duodenal and gastric ulcers compared with blood pressure in cases of cholecystitis (females).

males do not show such a marked fall as those in cases of duodenal ulcer; the difference between the blood pressures in this group and in the insurance group varies from 1.8 to 9 mm., and shows a significant difference only between the ages of 45 and 59. The difference between the blood pressure in the control cases and in cases of duodenal ulcers in males varies from 0.6 to 9.3 mm. and is not significant at any point. Comparison of the cases of gastric ulcers with the control cases, in

5. Pearl, Raymond: Medical Biometry and Statistics, Philadelphia, W. B. Saunders Company, 1923, p. 209.

males, shows even less difference in blood pressure; it ranges from 0.1 to 7.2 mm., and has no significance. The blood pressures in the control cases have a tendency to drop at from 25 to 35 years of age; this tendency is similar to that seen in the cases of gastric and duodenal ulcer, although cases of ulcer were excluded from the control group. On the other hand, the blood pressure curve of the life insurance cases rises steadily throughout.

In chart 2, which applies to female patients, there is not a point in the whole curve in which the difference in blood pressure is significant between the cases of duodenal or gastric ulcers and the life insurance cases. Unlike that in the males, the curve of the mean blood pressure

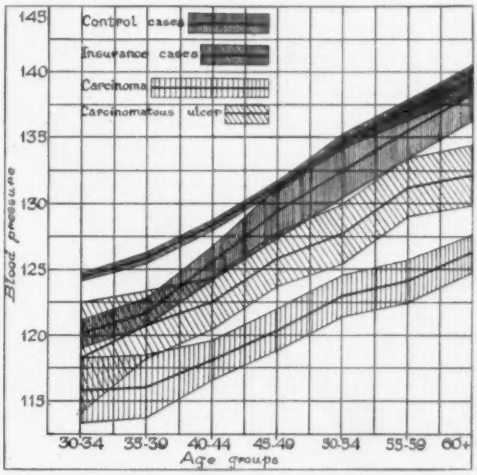

Chart 6.—Systolic blood pressure in cases of carcinoma of the stomach and carcinomatous ulcers compared with blood pressure in control cases and life insurance cases (males).

even rises above the one shown in the insurance curve at some points. Comparing the blood pressures in females with duodenal or gastric ulcer with the blood pressures in the control cases results are obtained that are similar to those found when blood pressures in female patients with duodenal or gastric ulcer were compared with the insurance cases, except that the blood pressure in the control cases is higher in later years and has a tendency to rise above the blood pressure in cases of ulcer throughout the whole curve. Although in females in the control cases, there is not the drop in blood pressure from the ages of 25 to 35 that is seen in the control cases in males, the averages remain level up to the age of 30.

The wide difference between the mean blood pressures of the male and female patients with gastric or duodenal ulcer in the later years of life is marked (chart 3).

Charts 4 and 5 show the blood pressure in cases of ulcer compared with that in cases of cholecystitis. The difference between the blood pressures in these two groups varies from 0.2 to 5.7 mm., and is not great enough at any point to be of significance. The probable errors even overlap each other most of the way. The

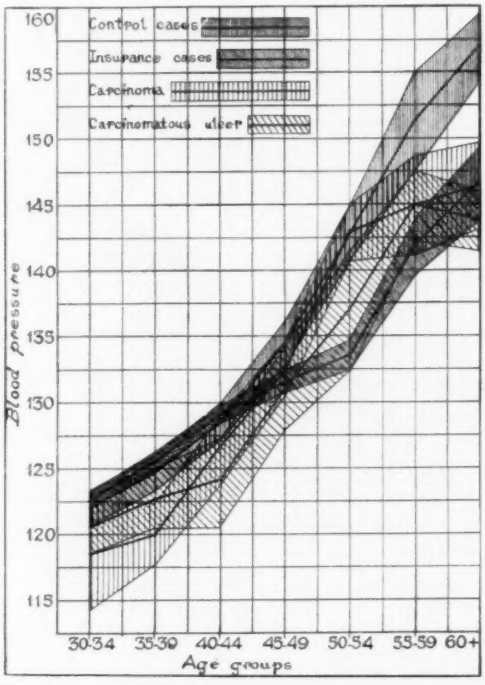

Chart 7.—Systolic blood pressure in cases of carcinoma of the stomach and carcinomatous ulcers compared with blood pressure in control cases and life insurance cases (females).

data in charts 4 and 5 furnish, perhaps, the most severe test on which to make the comparison to determine whether or not the systolic blood pressure is lowered in cases of gastric and duodenal ulcer. In cholecystitis, blood pressure is expected to be higher because of the tendency to obesity and the plethoric body type that is usually characteristic of persons with disease of the gallbladder. If the blood pressure in gastric and duodenal ulcer, on the one hand, and in cholecystitis, on the other,

should prove to be about equal, the inference would be that the blood pressure in gastric and duodenal ulcer is not lower than the so-called average blood pressure. Although in males the blood pressures in the cases of ulcer tend to be lower than those in either the insurance or control cases, and although in females they tend in the cases of ulcer to be lower than those in the control cases, yet the blood pressures in cases of ulcer do not vary greatly from those in cases of cholecystic disease. The difference in blood pressure between the two groups ranges only from 0.2 to 5.7 mm. Patients with cholecystic disease show a tendency toward obesity and toward apparently higher blood pressure, but this figure is lowered through the correction for weight. On the contrary, in cases of ulcer the patient tended toward emaciation,

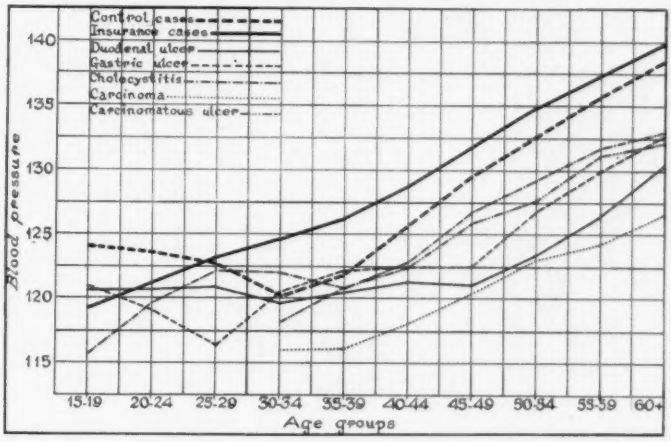

Chart 8.—Systolic blood pressure in cases of duodenal and gastric ulcers, cholecystitis, carcinoma of the stomach, carcinomatous ulcers of the stomach, control cases and life insurance cases (males).

and so the figures representing their blood pressures were raised by the correction for weight. Therefore, the difference that did exist between the uncorrected curves for blood pressure in ulcer and in cholecystitis was narrowed considerably by the correction for weight.

Charts 6 and 7 present the mean blood pressure in cases of inoperable carcinoma of the stomach and of carcinomatous ulcer, compared with that in the life insurance and control cases. As in cases of ulcer, the blood pressure in males in the cases of carcinoma of the stomach is much lower than that in the insurance group (chart 6); the difference between the values in these two groups varies from 8.5 to 13.2 mm., which is significant from the age of 40 on. In carcinomatous ulcers,

the blood pressure is higher, falling not more than 7.4 mm. below that in the insurance cases, and without significant differences in the whole curve. In comparison with the blood pressure in the control cases (from which the cases of carcinoma were excluded) there is a tendency to lower blood pressures in carcinoma, but this is of significance only in the last age group. The blood pressure curve in carcinomatous ulcer lies almost midway between that of the control cases and that of the cases of carcinoma of the stomach, and does not have any significant variation from the curve of the control cases.

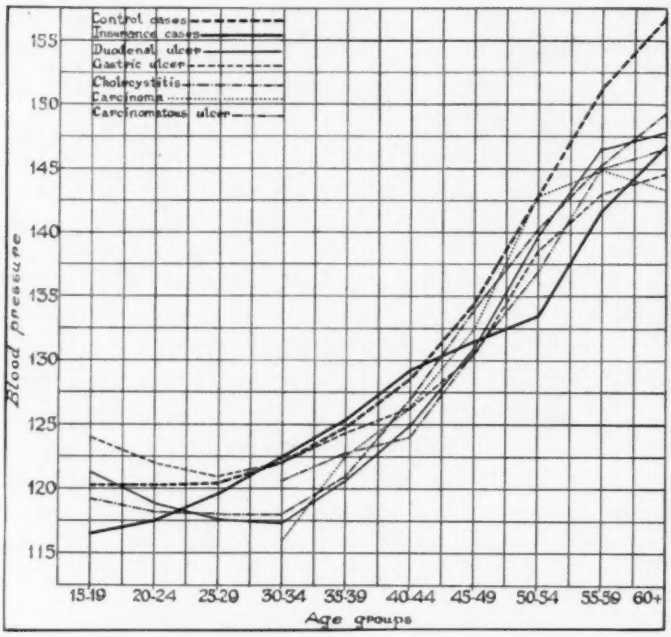

Chart 9.—Systolic blood pressure in cases of duodenal and gastric ulcers, cholecystitis, carcinoma of the stomach, carcinomatous ulcers of the stomach, control cases and life insurance cases (females).

The blood pressures of the female patients with inoperable carcinoma of the stomach and with carcinomatous ulcers follows the life insurance curve closely, and even rises above it from the ages of 45 to 59. The difference between the blood pressures in the insurance group on the one hand, and in the carcinoma and carcinomatous ulcer group, on the other hand, varies from 0.2 to 9.3 mm. and is not significant at any point. The mean blood pressure in the cases of carcinoma of the

stomach in females does not fall below that in the cases of carcinomatous ulcer, as it did in the males. The difference between blood pressure in cases of carcinoma of the stomach and that in the control cases varies from 0.1 to 13.6 mm., but is not significant because of the large probable errors. The blood pressures in cases of malignant ulcers vary less from those in the control cases, and the variations are not significant.

Chart 8 is a condensed graph drawn from the means of all of the blood pressure curves of the males. All of the curves are below that derived from the insurance cases from the age of 20 on, with the

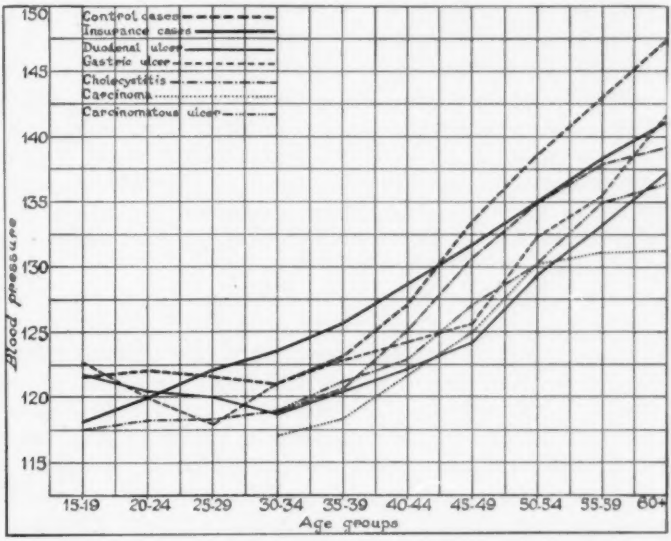

Chart 10.—Systolic blood pressure in cases of duodenal and gastric ulcers, cholecystitis, carcinoma of the stomach, carcinomatous ulcers of the stomach, control cases and life insurance cases (males and females combined).

curves from the cases of carcinoma of the stomach and of duodenal ulcer falling lowest. The same tendency to low blood pressures in all of the groups of persons with disease shows up well on the graph, with a range of not more than 8 mm. of difference between them. The curves also fall below those derived from the control cases, except for the ages from 30 to 40.

Chart 9 shows curves computed from the means of all of the blood pressure curves of the females. Here, as in chart 8, the same tendency exists among the curves of groups of patients with disease; all these curves adhere closely and rise above the insurance curve in the later

years of life, but they fall below the curves of the control cases except in the early years.

Wide differences between the mean blood pressure of males and of females were found in the control cases, and in cases of cholecystic disease, carcinoma of the stomach and malignant ulcer, as well as in cases of duodenal or gastric ulcer. This difference would show up even more plainly if these curves were placed side by side with curves derived from examination of applicants for life insurance; in life insurance work, the average blood pressure of the females is not higher than that of the males. In other words, in groups in which the majority of the subjects are diseased, blood pressures of the sexes vary, whereas in groups in which the majority of the subjects are healthy, this variation is not seen.

Chart 10 shows curves constructed from the combined mean blood pressures of males and females in each of the various groups studied. The largest difference between any two of these curves is 16.5 mm.; all curves from the age of 25 on fall below that constructed from the life insurance material, and from the age of 35 on below that of the control cases. The low tendency prevails because of the fact that there were more males than females in all of the groups studied except in the group with disease of the gallbladder.

SUMMARY

The blood pressure in cases of duodenal and gastric ulcer, compared with the curve constructed from life insurance statistics, is lower in males and in the sexes combined, but it is not lower in the females alone. Too much stress, however, cannot be placed on this comparison, because of the fact that the insurance cases were not corrected for weight, and the other groups were not corrected against a normal blood pressure, but against a control group. The blood pressures in this control group also are higher than those in the ulcer group in both males and females, but the variation is not of significance; the curves remain fairly parallel throughout all ages.

In comparing the blood pressure in cases of duodenal and gastric ulcer with that in cases of cholecystitis and carcinoma of the stomach or carcinomatous ulcer, the difference is not significant in either males or females. From this it must be concluded that in cases of ulcer the blood pressure is not particularly low, and is similar to that in other diseases of the alimentary tract. It might have been better to make the comparisons with other than gastro-intestinal diseases, but it would seem that the inclusion of a series of cases of cholecystic disease for comparison establishes the results as reliable, since the impression is almost universal that patients with cholecystitis have a tendency toward higher blood pressure.

If the data had not been corrected for weight, the results would have been somewhat different, and the comparison between the cases of ulcer or carcinoma with the cases of disease of the gallbladder might have been significant. The correction for weight, however, must be given consideration, for age and weight play an important part in the readings of blood pressure.

INFLUENCE OF THE DIAPHRAGM ON THE ESOPHAGUS AND ON THE STOMACH *

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In the anesthetized dog, two different types of contraction were noted when the cardia was examined by the insertion of the finger into the esophagus through a gastrostomy opening.[1] One type of contraction (the esophageal) was circular and constricting; it was reproduced at will by stimulation of the peripheral end of the vagus, and also by stimulation of the esophagus itself at any level above the gastro-esophageal junction. The second type, which was due to the contractions of the diaphragmatic pillars, was a progressively downward milking contraction and was coincident with each inspiration. The diaphragmatic contraction became more pronounced when diaphragmatic breathing became more forcible. The maximum contraction was noticed when the diaphragmatic crura were stimulated with the faradic current.

Clinical evidence of a relationship of the diaphragm to the cardia was brought out by Chevalier Jackson [2] and Tucker.[3] Jackson stated that the "diaphragmatic pinchcock or hiatal narrowing is both anatomical and functional. The peculiar arrangement of the tendinous and muscular structure of the diaphragm acts on this hiatal opening, pinching the esophagus shut in a way similar to that of the pinchcock that closes the rubber tube of the burrette in the laboratory. There are also special bundles of muscle fibers extending from the crura of the diaphragm and surrounding the esophagus, which contribute to the tonic closure and the coordinate opening in the deglutitory cycle and probably also in the emetic cycle." In an anatomic dissection of the diaphragmatic crura in the dog and in the human being, several important facts have been noticed. There is a more intimate relationship between the diaphragm and the gastro-esophageal junction (cardia) than is generally shown in illustrations of anatomic monographs and texts. The structure of the muscle fibers in the diaphragmatic pillars bears a greater resemblance

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* From the Department of Surgery, University of Illinois College of Medicine.

1. Joannides, Minas: The Relation of the Hiatus Esophageus of the Diaphragm to the Stomach, Arch. Int. Med. **43**:61 (Jan.) 1929.

2. Jackson, Chevalier: The Diaphragmatic Pinchcock in So-Called Cardiospasm, Laryngoscope **32**:139, 1922; Bronchoscopy and Esophagoscopy, ed. 2, Philadelphia, W. B. Saunders Company, 1922, pp. 71, 73 and 333.

3. Tucker, G.: Diaphragmatic Pinchcock in Health and Disease, M. Clin. North America **8**:931, 1924.

to the anal sphincter than it does to the rest of the diaphragm. A thin layer of areolar tissue separates the pillars from the cardia. This areolar tissue is definite in the human being and produces a definite line of cleavage between the esophagus and the pillars. On the other hand, in the dog this layer is very thin, so that one receives the impression that the fibers of the pillars are in direct apposition with the cardia. Anteriorly the muscle fibers of the pillars surround the stomach and esophagus in a manner similar to the fibers of the anal sphincter. As these fibers extend posteriorly to the esophagus and stomach, they decussate and become attached to the vertebrae. At the point of decussation the pillars form an inverted triangle which is small in the dog and from 1 to 2 cm. wide in the human being. The sides of this triangle are joined together by means of thin fibrous tissue. It is through this fibrous tissue that air may find its way from the mediastinum to the retroperitoneal tissues in mediastinal and interstitial emphysema.[4] Regarding the relation of the so-called cardiospasm to the diaphragm, Jackson stated that the so-called cardiospasm probably covers a number of diseased conditions, some functional, others organic, but none of them at the cardia. He gave a number of terms for cardiospasm in an attempt to specify more clearly the mechanism of the syndrome. So-called cardiospasm, according to Jackson, may be called preventriculosis, ingluviosis, functional hiatal stenosis, hiatal esophagismus, phrenospasm and diaphragmatic pinchcock stenosis. Jackson found "no sphincteric muscular arrangement at the cardiac orifice of the esophagus, so that spasmodic stenosis at this level is not possible and the term cardiospasm is, therefore, a misnomer." The observations of Jackson were corroborated by Mosher and McGregor.[5] In cases of so-called cardiospasm they found a fibrosis in the pillars, an absence of an anatomic sphincter of the cardiac end of the esophagus and a decrease of the ganglion cells of Auerbach's plexus.

Although this study bears a definite relation to the mechanics of so-called cardiospasm, it deals primarily with the rôle played by the diaphragm in the normal contraction and relaxation of the cardia, in the mechanics of belching and in the induction of peristaltic contractions in the stomach.

EXPERIMENTAL WORK

Observations were made by placing a normal subject in an oblique upright position with the right shoulder placed against the fluoroscopic screen, after the method described by Carman.[6] A barium meal was

4. Joannides, M., and Tsoulos, G.: Experimental Production of Mediastinal and Interstitial Emphysema in the Dog, to be published.

5. Mosher, H. P., and McGregor, G. W.: A Study of the Lower End of the Esophagus, Ann. Otol. Rhin. & Laryng. **37**:12 (March) 1928.

6. Carman, R. D.: The Roentgen Diagnosis of Diseases of the Alimentary Tract, ed. 2, Philadelphia, W. B. Saunders Company, 1921, p. 44.

then given. When the barium was seen to reach the cardia the patient was asked to breathe deeply. With each inspiration the esophagus was constricted at the cardia to such a degree that no barium could be seen below the diaphragm. A ballooning of the filled esophagus resulted above this constriction. This constriction and ballooning corresponds, in certain respects, with the roentgen pictures of so-called cardiospasm. It also no doubt corresponds with the terminal phase of the downward milking contraction in the cardia of dogs that was observed by insertion of the examining finger through an opening in the stomach. This contraction, however, is transitory, because with the onset of the expiratory phase of respiration the diaphragm was noticed to rise and, coincidentally with this relaxation, the barium ran freely again into the stomach. This phenomenon could be repeated as often as desired in the same patient or in different patients. Some variations were noticed, depending on the movements of the diaphragm and the tendency of the patients to dyspnea. In persons who could hold their breath fairly long, the barium remained above the diaphragmatic level longer than in those who could not. In persons who showed hypertonicity and a tendency to spasm there was a delay in the course of the barium at the cardia even during expiratory relaxation. If the patient was asked to take a few deep breaths, thus inducing milking contractions at the pillars, this spasm could be relieved and the barium found its way into the stomach. If the barium meal was distasteful to patients and there was fluoroscopic evidence of a tendency to nausea and vomiting, relief was given by making the patient take a few long deep breaths. After a few deep breaths, he showed a normal condition in the esophagus, diaphragm and stomach.

With the introduction of barium into the stomach in the majority of patients, a large air bubble finds its way into the stomach. With the patient in the erect position the air bubble floats on the surface of the gastric fluids and distends the fundus. This phenomenon afforded an opportunity for study of the mechanism of belching as seen with the fluoroscope. When the patient made a conscious effort to belch, the costal portion of the diaphragm contracted and the vertebral portion relaxed. In the meantime, the abdominal muscles contracted and squeezed the stomach, at the midportion of which a constricting band had developed by this time, causing it to assume the shape of an hourglass. When the patient was ordered to belch again, one could see a series of peripheral diaphragmatic contractions and a relaxation of the vertebral portion with the air moving away from the dome of the fundus and closer to the cardiac opening. Jackson mentioned the presence of a "kink of the esophagus" which normally prevents regurgitation when a man with a full stomach stands on his head or inverts his body.

That such a deflection or kink is present can be demonstrated by watching the course of the barium through the esophagus into the stomach. The barium travels straight downward, deviating slightly at curves of the spine; when it reaches the cardia it suddenly deflects from its course along the spine in an angle of from 30 to 50 degrees. It is possible, therefore, that in belching the contractions of the diaphragm push the fundus down and medially and thus release the kink that is formed at the junction of the cardia and the fundus.

In some cases in which repeated attempts at induced belching failed, it was noticed that the whole left side of the diaphragm would relax for a moment and at the same time the right side would contract coincidentally with the contractions of the abdominal wall and stomach. Contractions and relaxations of the diaphragm, as seen normally with inspiration and expiration, have no apparent relation to belching. No belching occurred either with deep inspirations or with forcible expirations. Similarly the air in the fundus could not be squeezed out by manual pressure over the abdomen. If a stomach tube was passed into the stomach, under such circumstances, air could be readily squeezed out. This observation has an important clinical application. Under varying conditions during an operation the stomach may become so distended with air that any external pressure over the exposed stomach will not force the air out. On the contrary, it may cause injury to the wall of the tensely distended organ. A tube introduced into the stomach from above will promptly cause the air to run out from the stomach, at times even without compression over the organ. Kelling [7] found the same condition in dogs under deep anesthesia. This phenomenon may be regarded as corroborative evidence that the constriction is due to a spasm of the diaphragmatic pillars in the region of the cardia, provided one assumes that Jackson's or Mosher and MacGregor's observation is correct, namely, that there is a pinchcock phrenospasm or that there is no actual sphincter in the esophagus at the cardia.

After the barium reaches the stomach, one can induce prompt contractions in the organ by having the patient take deep breaths. Such peristaltic waves in the stomach may be central in origin and induced reflexly from cross stimuli from the respiratory center to the vagus center. It appears more reasonable to assume, however, that such an induction of peristalsis in the stomach depends on the milking contractions in the pillars with the impulses probably extended along the wall of the stomach or perhaps is due to the intermittent increase and decrease of intragastric pressure induced by the contractions of the diaphragm.

7. Kelling, G.: Ueber den Mechanismus der acuten Magendilatation, Arch. f. klin. Chir. **64**:393, 1901.

COMMENT

The experimental work on the anesthetized dog and the clinical results with the fluoroscopic examinations of normal patients show convincingly that the diaphragm plays an important rôle in the mechanics of contractions and relaxations of the esophagus at the cardia.

The classic work of Cannon [8] on the activities of the esophagus must be mentioned. He stated that two activities of the cardiac sphincter are to be distinguished: a persistent state of tonus, and, at times superposed on this, rhythmic alternation of contraction and relaxation. He further stated that "normally we are unconscious of the nauseating odor and the highly disagreeable taste of the gastric contents, and for this pleasant security the closed cardia is highly responsible. As aids in establishing this barrier between the stomach and the gullet, the sharp angle between the two structures, acting like a valve, and the close grasp of muscle layers in the diaphragm have been mentioned."

The present results are not in accord with the assumptions of Alvarez.[9] After mentioning the work of Gubaroff, Kelling, Sinnhuber and Caballero, who felt that a large part of the sphincteric action at the cardia must be due to the contraction of the diaphragmatic fibers surrounding the lower end of the esophagus, he stated that "this now seems improbable because it can be seen with the roentgen ray that the sphincter is generally situated some two centimeters below that point." Alvarez did not state how he determined the presence of such a sphincter below the diaphragm. The dissection of cadavers and dogs in the present experiments showed that the pillars are directly over the junction of the stomach and esophagus. The fluoroscopic observations corresponded with the bronchoscopic observations of Jackson and Tucker. Knowing from digital examinations of the esophageal orifice that there is a milking contraction, and seeing the extent of such a contraction under the fluoroscope, I feel justified in assuming that Jackson's pinchcock contraction of the diaphragm is probably only one phase of a complex contraction.

The rôle of the diaphragm in voluntary belching is of great interest. The peculiar contractions of the costal fibers of the diaphragm tend to straighten the kink just below the cardia and allow the air to be squeezed out. These peripheral contractions probably also induce a pull on the vertebral portion of the diaphragm and thus cause a dilatation of the pillars. Coincident with these contractions, the abdominal muscles and the stomach induce belching. It is interesting to note that when a barium meal is taken (1 part barium sulphate and 3 parts malted milk plus

8. Cannon, W. B.: The Mechanical Factors of Digestion, New York, Longmans, Green & Company, 1911, p. 33.

9. Alvarez, W. C.: The Mechanics of the Digestive Tract, ed. 2, New York, Paul B. Hoeber, 1927, p. 91.

water), invariably a large air bubble enters the stomach and promptly lodges itself in the fundus immediately under the diaphragm. This air undoubtedly stays lodged either in the esophagus or in the buccal cavity and is pushed down into the stomach by the weight of the fluid. Repeated examinations before a barium meal failed to show the presence of air in the empty stomach. Therefore, this air must necessarily come from above the stomach. It is undoubtedly this same phenomenon that one encounters in the feeding of infants. A gas bubble enters the stomach of an infant and may distend the stomach causing colic or prevent the child from taking the necessary amount of milk at each feeding. A roentgenologic study of infants during feeding and immediately afterward may solve the problem of finding a means to expel swallowed air by more reliable methods than those in present usage.

SUMMARY

1. Two types of contraction can be observed by a digital examination of the cardia, namely, a circular constricting contraction and a downward milking contraction.

2. Fluoroscopic examination of the course of barium in the stomach reveals an obstruction in the region of the cardia coincident with each inspiration, and a relaxation with release of the obstruction with each expiration.

3. The obstruction noticed fluoroscopically may correspond to a single phase of the downward contraction and is, no doubt, indentical with the pinchcock contraction described by Jackson.

4. Belching is accomplished by the coordinate contraction of the abdomen, the stomach and the costal end of the diaphragm, with the relaxation of the vertebral end.

5. Spasm of the diaphragmatic pillars with obstruction and dilatation of the esophagus may be relieved by deep inspirations and expirations.

6. Acute sudden gaseous distention of the stomach in patients during operations under ethylene, nitrous oxide or ether anesthesia may be easily relieved by intubation of the stomach.

7. Gastric peristalsis was noticed to start as a result of deep breathing.

8. So-called cardiospasm may be an exaggeration of the normal contractions of the diaphragmatic pillars. A persistent spasm of these bundles will, no doubt, cause a chronic obstruction at the cardia.

OPIUM ADDICTION

X. THE EXCRETION OF MORPHINE BY HUMAN ADDICTS*

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The relation between the capacity of the animal body to destroy morphine and its power of developing tolerance to the drug following repeated dosage has been of interest to pharmacologists for many years. Recent study with the aid of improved chemical methods indicates that Faust's [1] conclusion, that a direct, casual relationship between the two phenomena exists, is incorrect. It seemed important to collect from human material such data as might bear on this subject. The study here reported concerns the excretion of morphine by human addicts; the difference between the amounts of morphine administered and those excreted is to be regarded as a measure of morphine destroyed.

While it is well known from the early observations of Kauzmann,[2] Vogt,[3] and Jacques [4] that morphine is eliminated in the urine and feces of human addicts, its quantitative excretion in these channels has, to our knowledge, not been studied. In the subjects whom we have studied it has been possible to control reliably the morphine dosage, to vary this at will and to collect the excreta quantitatively. In addition to observations on the (healthy) subjects of uncomplicated addic-

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* Expenses of this research were defrayed by the Committee on Drug Addictions, New York City, and this work carried out under the guidance of the Philadelphia Committee for the Clinical Study of Opium Addiction, in the wards of the Philadelphia General Hospital, which were placed at our disposal through the courtesy of the Director of Public Health, City of Philadelphia, and also the Laboratory of Pharmacology of the University of Pennsylvania.

1. Faust, E. S.: Ueber die Ursachen der Gewohnung an Morphin, Arch. f. exper. Path. u. Pharmakol. **44**:217, 1900.

2. Kauzmann: Beiträge für den gerichtlich chemischen Nachweis des Morphins und Narkotins in thierschen Flussigheiten und gemehen, Inaug. Dissert., Dorpat, 1868. Cited by Faust (footnote 1, p. 223).

3. Vogt: Arch. d. Pharm. **7**:23 (July) 1875.

4. Jacques: Thèse Bruxelles, 1880; Essai sur localization des alcoloides dans le foie, cited by Faust (footnote 1, p. 224).

tion, we had the opportunity of measuring the elimination of morphine, on constant dosage, during the periods of fever, crisis and convalescence in one addict who was acutely ill with pneumonia.

METHODS AND PROCEDURE

As soon as possible after admission the predetermined morphine regimen was established. The daily dosages of morphine chosen were 15, 30 and 60 grains (0.97, 1.94 and 3.89 Gm.), and a period of four days was ample to establish any one of these levels, regardless of the amounts which had been taken before admission or the form of the drug used. Experimental periods usually lasted for five days, although one case was studied for only three days and another for four days. No attempt was made to control the diet, nor were any other drugs administered except an occasional saline cathartic to obtain a bowel movement.

Morphine in urine was determined by extraction with chloroform-alcohol solvent, purification through further extractions and final precipitation with silicotungstic acid.[5] When the quantity of morphine in the final extract was less than 10 mg., it was estimated colorimetrically by the diazo-reaction.[6]

The suitability of this procedure for human material was shown by a series of control experiments. From 100, 200, 250 and 280 cc. volumes of normal urine, analyzed gravimetrically, recoveries of added morphine were from 92 to 97.7 per cent. The morphine silicotungstate yielded, after ignition, from 70 to 70.3 per cent of oxide residues, an indication of the almost complete purity of the morphine precipitate. Similar controls containing no morphine showed negligible turbidity with silicotungstic acid. Colorimetric control experiments gave from 98 to 100 per cent recoveries of added morphine, with satisfactory blanks. These results were obtained only after meticulous attention to detail, as described by one of us (W. A. W.)[7] in a study of the elimination of morphine in dogs. The numerous possibilities of error in morphine analysis made it necessary to check and recheck every step in the procedure at frequent intervals.

Many of the specimens of urine were analyzed both colorimetrically and gravimetrically. Typical results shown in table 1 indicate the consistency of the two methods.

Feces, after preliminary acidification and evaporation over the steam bath, were analyzed as previously described.[5] Results on control determinations were variable and unsatisfactory. Hence, the figures presented for fecal excretion are hardly more than qualitative indications that a relatively small amount of morphine appears in the feces.

RESULTS AND COMMENT

Table 2 contains the results of the quantitative excretion of morphine in the urine and feces of a series of addicts receiving 15, 30 or

5. Balls, A. K., and Wolff, W. A.: The Determination of Morphine, J. Biol. Chem. **80**:379 (Dec.) 1928.

6. Lautenschlager, L.: Arch. d. Pharm. **257**:13, 1919. Plant, O. H., and Pierce, I. H.: Excretion of Morphine During Gradually Produced and Prolonged Tolerance to Morphine in Dogs, J. Pharmacol. & Exper. Therap. **31**:212 (June) 1927.

7. Wolff, W. A.: The Elimination of Morphine in Dogs, to be published.

60 grains per twenty-four hours. Sixteen studies were made on ten different patients. One patient (case 3-29) was studied on all three levels: he eliminated 7.9, 8.2 and 10.3 per cent, respectively, in the urine. Cases 10-29 and 2-29 were each studied on two different levels. The patient in case 10-29 eliminated 8.6 per cent in the urine while receiving 30 grains, and 7.7 per cent on a 60 grain level. Likewise in case 2-29 there was little variation in the percentage of morphine eliminated. While receiving 15 grains he excreted 10.1 per cent, and while receiving 60 grains, 12.2 per cent.

Case 6-29 was studied on the same level of 30 grains at two different intervals, with the elimination of 8.8 and 9.5 per cent of the morphine administered.

Five patients who were maintained on 15 grains (0.97 Gm.) daily varied from 6.5 to 10.1 per cent of excretion. Urinary excretion of morphine for seven patients on a constant dosage of 30 grains ranged

TABLE 1.—*Comparative Results of Colorimetric and Gravimetric Methods in Analysis of Urine for Morphine*

Case	Colorimetric Method, Mg. per 100 Cc.	Gravimetric Method, Mg. per 100 Cc.
5-29	4.7	4.1
12-29	32.7	32.0
4-29	6.1	7.8
10-29	8.2	9.3
10-29	15.0	15.3
3-29	9.2	8.4
3-29	22.0	18.8

from 8.2 to 12.9 per cent. Morphine recovered from the urine of four patients receiving 60 grains per day varied from 7.7 to 12.2 per cent. It may be noted that the percentage of morphine eliminated in the feces analyzed never exceeded one-fourth the urinary percentage. Absolute values were too uncertain and variable to justify general conclusions.

The results obtained in the foregoing experiments on healthy addicts show that regardless of the amounts taken, the fraction eliminated in the urine is remarkably constant. Averages of the percentage of urinary excretion on the 60, 30 and 15 grain dosages amounted to 10.7, 9.8 and 8.7 per cent, respectively. The fraction eliminated bears no relation to height, weight, volume of urine or length of addiction, but is directly proportional to the quantity administered. These results show clearly that in human addicts the amount of morphine destroyed is proportional to the amount absorbed. Despite the existence of mechanisms for the disposal of morphine, there must still be present in the addict an increased tissue tolerance, since the patients receiving 60 grains a day were eliminating in the urine approximately

6 grains (0.388 Gm.), and those on 30 grains approximately 3 grains (0.194 Gm.).

The lethal dose of morphine for man is not definitely stated in textbooks of pharmacology. Kunkel [8] quoted the minimal lethal dose as 1½ grains (0.097 Gm.), but added that under favorable circumstances a person might recover from 15 grains. He regarded, however, the prognosis from a dosage of over 4 grains (0.259 Gm.) as decidedly unfavorable. Sollmann [9] stated that the lethal dose ranges

TABLE 2.—*Data Obtained from Patients During Periods of Addiction*

Case	Age, Years	Period of Study, Days	Average Weight		Average Daily Urine for Period, Cc.	Daily Administration of Morphine		Average Daily Excretion			
								Urine			Feces, per Cent
			Pounds	Kg.		Gm.	Mg.	Grains	Mg.	Per Cent	
1-29	36	5	189	87.0	1,700	15	972	1.50	97	10.0	2.2
2-29	32	3	123	61.3	1,468	15	972	1.51	98	10.1	3.0
3-29	36	5	136	62.6	865	15	972	1.16	76	7.9	...
4-29	39	5	113	52.0	1,217	15	972	1.17	77	7.9	...
5-29	46	5	133	61.3	1,424	15	972	0.97	63	6.5	...
6-29	35	5	122	56.2	2,332	30	1,944	3.24	168	8.8	...
7-29	39	5	156	71.8	1,652	30	1,944	4.04	210	10.6	3.5
8-29	40	5	120	55.3	869	30	1,944	3.88	252	12.9	1.7
3-29	36	5	138	63.5	1,602	30	1,944	2.46	160	8.2	1.0
10-29	30	4	154	70.9	1,806	30	1,944	2.57	167	8.6	3.3
6-29	35	5	126	58.0	1,808	30	1,944	2.83	184	9.5	...
9-29	34	5	150	69.1	2,841	30	1,944	3.14	204	10.5	...
10-29	30	5	156	71.8	1,976	60	3,888	4.62	300	7.7	0.9
2-29	32	5	137	63.1	1,707	60	3,888	7.29	473	12.2	0.6
3-29	36	5	140	64.5	1,957	60	3,888	6.15	399	10.3	0.3
12-29	30	5	133	61.3	1,357	60	3,888	6.71	435	11.2	...

TABLE 3.—*Morphine Recovered in Urine Following Abrupt Withdrawal of the Drug*

Case	0-2 Hours, Mg.	2-4 Hours, Mg.	4-6 Hours, Mg.	6-8 Hours, Mg.	8-10 Hours, Mg.	10-12 Hours, Mg.	12-16 Hours, Mg.	16-20 Hours, Mg.	20-24 Hours, Mg.	24-30 Hours, Mg.
9-29*	40.1	11.5	9.6	8.5	6.6	4.9	5.6	5.0	4.0	11.2
6-29*	26.7	11.2	9.0	5.6	5.5	3.5	0.7	3.3	4.2	6.8

* Received 30 grains (1.944 Gm.) of morphine sulphate daily, 5 grains (0.324 Gm.) at four hour intervals. The last injection was given at 9 a. m. The six hour period immediately following readministration of 5 grains (0.324 Gm.) of morphine sulphate resulted in a recovery of 49.6 mg. in case 9-29, and in a recovery of 52.1 mg. in case 6-29.

between 3 and 6 grains, but mentioned one case of recovery from 60 grains. He also regarded the prognosis unfavorable when the dosage was more than 4 grains.

Table 3 and chart 1 contain the results of the analysis of urine collected at two hour intervals for the first twelve hours, four hour intervals for the second twelve hours and a final six hour period,

8. Kunkel, A. J.: Handbuch de Toxikologie, part 2, Jena, Gustav Fischer, 1901, p. 803.

9. Sollmann, Torald: A Manual of Pharmacology, ed. 3, Philadelphia, W. B. Saunders Company, 1926, p. 300.

during thirty hours of abrupt withdrawal. In each case the last hypodermic injection of morphine sulphate given was 5 grains (0.324 Gm.).

The rate of elimination of morphine in the urine following the abrupt withdrawal in the two cases represented in both table 3 and chart 1 showed a rapid fall during the first four hours, after which a more constant level was maintained.

The rapid decrease in excretion during the first four hours was also noted in short period experiments for six hours following a dose of 5 grains of morphine sulphate. The morphine eliminated during the first two hours was three times that eliminated during the fifth and sixth hours. During withdrawal, the patient in case 9-29 eliminated 0.051 Gm., or slightly less than a grain, in the first four hours, 0.15 Gm. for the four to eight hour interval, or slightly more than

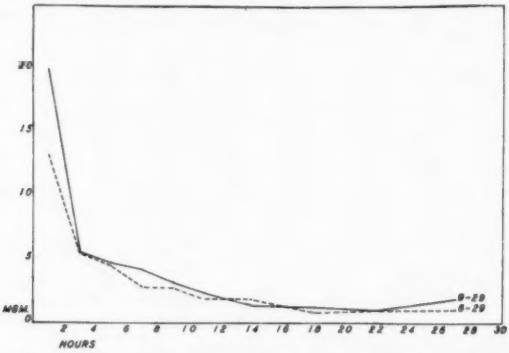

Chart 1.—Curve of morphine excretion in the urine (cases 9-29 and 6-29) at two hour intervals following abrupt withdrawal of the drug for thirty hours. The total amount of morphine given twenty-four hours prior to withdrawal was 30 grains (1.944 Gm.). The last single dose was 5 grains (0.324 Gm.).

one-fourth grain, and then an hourly average of about a thirtieth of a grain during the rest of the experiment. During withdrawal, the patient in case 6-29 eliminated about 0.040 Gm. the first four hours or a little less than two thirds of a grain, one-fourth grain for the next four hours, and an hourly average of a fortieth of a grain for the rest of the experiment. Both addicts had been receiving 5 grains every four hours and, each time the administration was due, showed the usual eagerness for the drug. When the interval was lengthened to eight hours, restlessness manifested itself and a dosage of one-fourth grain given at this time had little effect. These curves, we think, show clearly a relationship between the rapidity of excretion of morphine and the desire for the next dose. As the total amount of drug in the body falls to a certain level, indicated by the change of rate of excretion about

the fifth hour, the patient shows an eagerness for the drug. If no drug is given at this time and that present in the body is further depleted, symptoms of withdrawal soon become evident.

Chart 2 contains the record of the temperature of the patient with pneumonia (case 11-29), as well as of the elimination of morphine during the various arbitrary periods and the total nitrogen during these same periods. Throughout the entire course of the disease and convalescence, he received 15 grains every twenty-four hour period. It will be noted that during the first three days of fever the patient eliminated in the urine 13.3 per cent of the total morphine given. Following the first three days of the fever the patient became desperately ill, and con-

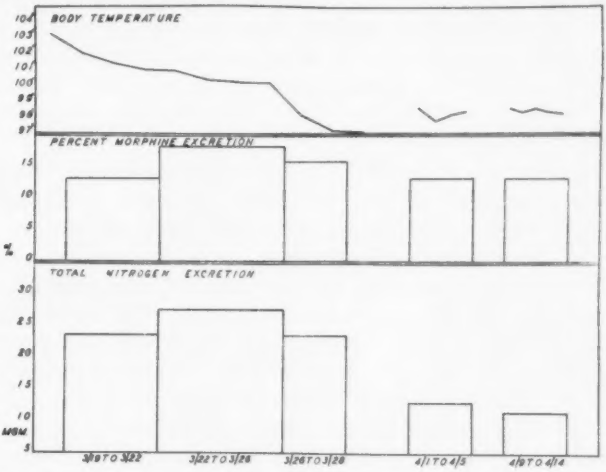

Chart 2.—Curve showing the bodily temperature and the excretion of morphine and total nitrogen in the urine per twenty-four hour period during the illness and convalescence of a human addict suffering with pneumonia. Fifteen grains of morphine was administered daily throughout the disease and convalescence.

tinued so for four days; during this time the elimination of morphine in the urine was 18.2 per cent of the amount administered. The crisis now ensued and during the following forty-eight hours only 15.7 per cent of the morphine appeared in the urine. A week later, during what we term the convalescent period, 13 per cent of the morphine given was recovered, and two weeks after the crisis the amount eliminated was still the same.

It is during the period just preceding the crisis in pneumonia that the various organs began to show cloudy swelling and degenerative processes; the urine in this case, however, remained remarkably free

from albumin. During this period the total excretion of nitrogen as well as the elimination of morphine rose. This relationship is striking. Increased elimination of nitrogen indicates a break-down of the tissues, while increased elimination of morphine probably indicates a decreased capacity for retaining or destroying the drug. Hence, as those tissues which normally retain or destroy morphine begin to degenerate, the kidneys eliminate the excess drug.

The prompt recovery of the addict while receiving the 15 grains daily throughout the period of illness and convalescence supports the belief in the harmlessness of the drug on organic functions when the body is accustomed to it. This statement may be challenged in this particular case and the question may be raised whether the patient might not have been less ill had he not been given the drug. However, realizing that withholding the drug from an addict always results in the appearance of symptoms of withdrawal and not wishing to add to the patient's suffering, we felt justified in continuing the drug to avoid the discomfort of withdrawal.

The general condition of the healthy addicts under these various dosages is of interest. It was not a difficult procedure to increase the dosage from 10 (0.648 Gm.) to 60 grains daily within two or three days. Practically all our patients showed a gain in weight in the hospital while receiving these various amounts. No symptoms of intoxication appeared during the administration of the large quantities. One patient showed a tendency to slight drowsiness when left absolutely alone, but any interesting event or conversation resulted in his immediate attention and participation. Sudden reduction from 60 to 30 grains resulted in a marked change of disposition; this was more marked in abrupt reduction from 30 to 15 grains, and was even worse in reduction from 15 to 7½ grains (0.486 Gm.). All patients subjected to this drastic reduction manifested marked changes in disposition. No symptoms of withdrawal were evident, except slight relief from constipation. The patients complained bitterly during this abrupt reduction, but we are convinced that this would have been avoided had not a certain familiarity developed between the patients and the observers during the progress of the experiment.

CONCLUSIONS

Quantitative estimation of the elimination of morphine in the urine of human addicts showed a remarkable constancy in ratio to the amounts administered. The daily administration of 15, 30 and 60 grains resulted in an average elimination of 8.7, 9.8 and 10.7 per cent, respectively. The length of addiction, quantities taken just prior to admission, age, weight and volume of urine did not influence this rate.

Fecal excretion of morphine fell far below the urinary level, but was too variable to justify general conclusions.

Abrupt withdrawal of morphine resulted in a rapid fall in urinary excretion during the first four hours, followed by a much lower and constant level for the next twenty-six hours.

The elimination of morphine in an addict suffering with lobar pneumonia, to whom 15 grains was administered daily throughout the illness and convalescence, showed the same level of excretion during the early part of the disease, following the crisis and during the convalescent period, but a rise in the period just before the crisis when he was critically ill. No unusual signs or symptoms appeared during the illness that could be attributed to the morphine.

OPIUM ADDICTION

XI. GENERAL SUMMARY *

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The narcotic problem is recognized today as one of the most important medical and sociologic problems confronting the medical profession. Although isolated studies on the problem have been made from time to time, no comprehensive investigation of its aspects, biologic, medical, social, economic and legal, has been consistently pursued until recent years. The Committee on Drug Addiction in affiliation with the Bureau of Social Hygiene, Inc., of New York has been engaged since 1921 in the study of this important problem. An extensive compilation of facts known and of views held with respect to opium addiction was made by Terry and Pellens [1] and published by the committee in book form. These inquiries demonstrated an urgent need for further investigation of the various phases of the problem by careful scientific methods, and accordingly the committee subsidized a number of field studies, experimentation in several university laboratories and a clinical study of the addict in the wards of the Philadelphia General Hospital.

The results of this clinical study have been published in a series of papers of which this is a brief summary.

The study was designed to determine whether objective investigations would reveal any changes that can be measured by physical, chemical or physiologic methods in the addict who is taking daily doses of from ½ to 60 grains (0.032 to 3.94 Gm.) of heroin or morphine that would differentiate him from a normal person, would serve to identify the state of opium addiction or would provide indications to guide in his rehabilitation.

It aimed furthermore to study by similar methods the addict during the period immediately after withdrawal of the drug at the time when he is suffering from "withdrawal symptoms." This characteristic train

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* From the Narcotic Wards of the Philadelphia General Hospital.

* Expenses of this research were defrayed by the Committee on Drug Addictions, New York City, and this work was carried out under the guidance of the Philadelphia Committee for the Clinical Study of Opium Addiction, in the wards of the Philadelphia General Hospital, which were placed at my disposal through the courtesy of the Director of Public Health, City of Philadelphia.

1. Terry, Charles E., and Pellens, Mildred: The Opium Problem, Camden, N. J., Haddon Craftsmen, 1925.

of symptoms consists, in about the following order, of yawning, lacrimation, sneezing, restlessness, sweating, hot flashes and chills, vomiting, diarrhea, cramps in the extremities and abdomen, muscular tremors, marked irritability, complaints of extreme weakness, loss of weight, marked pilomotor activity, rarely diplopia and occasionally death. These symptoms reach their height at the end of about seventy-two hours following the withdrawal of the drug, and with the exception of occasional complaints of weakness, gradually subside in from five days to two weeks. Readministration of morphine in the amounts usually taken or in smaller amounts will within from five to thirty minutes bring about complete relief from all these symptoms. The addict professes to feel normal again with regained strength.

After successful withdrawal when the drug has been withheld for from ten days to two weeks the addict is taking food normally, has regained his weight and presents the picture of well being. If he should now revert to the drug, he will never start with more than ⅛ or ¼ grain (0.008 or 0.016 Gm.) of heroin or morphine, larger amounts than this causing toxic symptoms and even death. The addict is again for the time being similar to normal persons in respect to tolerance. A group of addicts at this period was studied by the same methods to detect any difference in them when their tolerance had disappeared.

Finally a study was made in collaboration with the Department of Pharmacology of the University of Pennsylvania on the excretion of morphine in the addict.

Our general method of approach in these studies has been as follows. A suitable addict having been selected on admission, his dosage of morphine was for a time continued hypodermatically in sufficient quantities to prevent the appearance of withdrawal symptoms. During this period of several days he was measured, weighed, his vital capacity was determined and he was allowed to remain about the ward. A standard series of studies was then carried out and designated as "during the addiction period." The drug was then abruptly withdrawn for forty-eight hours, the patient being carefully watched and observed during this period. At the end of this time, the same series of studies was again made. He was now given sufficient morphine to bring about complete relief. Again the same studies were carried out. Within a day or two the hyoscine method of treatment was employed, and at the end of about ten days when the patient was ready for discharge from the hospital and said that he was feeling well, the series of studies was again carried out.

Our investigations were readily made during addiction and following treatment but met with many failures during withdrawal, as the patients often refused to cooperate. In the first paper of the series, we have

described the type of addict with which we have dealt and have pointed out some of the precautions which must be observed to avoid being deceived by the addict's tricks to obtain drug and by his tendency to simulate a state of either suffering or of well being as may best serve his purposes.

RESULTS OF STUDIES

The results may be summarized as follows:

In a series of opium addicts who were given morphine in sufficient quantities to prevent withdrawal symptoms, a study of the pulse rate and blood pressure while the subjects were standing and again while they were reclining, of the respiration, electrocardiograms and the response to staircase climbing tests, resulted in the finding of no marked deviation in the behavior of the circulation and respiration from that of normal persons.

In 70 per cent of the cases the average pulse rate while the subject was reclining was slightly below the usual average figures given for normal persons.

Orthodiagramatic measurements showed a tendency to a smaller size for the heart than the average for normal persons.[2]

A series of addicts receiving morphine sulphate hypodermatically has been studied with respect to the following: hemoglobin, red blood cell count, white blood cell count, differential count, sedimentation rate, blood viscosity, cell volume, Wassermann reaction, specific gravity of the blood and plasma, plasma refractive index, dry matter of the blood and plasma, plasma p_H, carbon dioxide capacity of the plasma, serum conductivity, sugar, urea, creatinine, uric acid, cholesterol, chloride and lactic acid of the blood and calcium, magnesium and phosphate of the serum.

In a general way there was a tendency for low red count, and high leukocyte count, but not uniformly in all cases. The cholesterol was usually increased and the phosphate diminished. The lactic acid was uniformly high. No other constituents showed any suggestive departure from the normal.

A slight degree of anemia may be present when the addict is forced to live in poor hygienic surroundings when all his funds are required to purchase the drug at the expense of sufficient nourishing foods.[3]

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2. Light, Arthur B., and Torrance, Edward G.: Opium Addiction: III. The Circulation and Respiration of Human Addicts During the Administration of Morphine, Arch. Int. Med. **43**:556 (April) 1929.

3. Karr, Walter G.; Light, Arthur B., and Torrance, Edward G.: Opium Addiction: IV. The Blood of the Human Addict During the Administration of Morphine, Arch. Int. Med. **43**:684 (May) 1929.

Studies of the stomach, kidney, liver, basal metabolism, thymus, temperature, dextrose response to epinephrine and to morphine revealed no fundamental differences in addicts who were administered morphine to supply their needs, except a slight delay in the average response of gastric secretion to a test meal, the presence of albumin in the urine in 17 per cent of the cases and wide fluctuations of the individual determinations of basal metabolism but an average metabolism within the normal limits. A delay in the return to normal of the blood sugar following the ingestion of dextrose by mouth was also noted.[4]

We have been unable to detect any marked physical deterioration or impairment of physical fitness aside from the addiction per se in the series of cases of opium addiction studied during the administration of morphine.

The existence of considerable emaciation in certain cases we believe to be caused by the unhygienic and impoverished life of the addict rather than by the direct effects of the drug.[5]

Abrupt withdrawal of morphine for twenty-four hours in four addicts resulted in the appearance of mild withdrawal symptoms. These symptoms were accompanied with slight negligible changes in the pulse rate, leukocyte count and basal metabolism rate. Changes in behavior and irritability would indicate that mental suffering begins before physical suffering.

Abrupt withdrawal of morphine for forty-eight hours from a series of ten addicts resulted in the appearance of rather severe withdrawal symptoms. One addict showed diplopia. These changes were accompanied by a definite leukocytosis in eight of the ten cases, concentration of the blood in all cases and a slight rise in cholesterol of the blood in seven. Albuminuria was found in two cases. The p_H of the blood, urea nitrogen and sugar showed no changes. Considerable loss of weight was found during the forty-eight hour withdrawal period.

Following the readministration of the drug and relief from subjective symptoms, the increased leukocyte count and concentration of the blood still remained, as did the diplopia and muscular twitchings of the face, for several hours. A rise in the percentage saturation of the oxygen of venous blood was noted in all cases following the readministration of the morphine. The circulatory changes noted were a slight increase in the pulse rate and a slight fall in systolic pressure. Staircase

4. Light, Arthur B., and Torrance, Edward G.: Opium Addiction: V. Miscellaneous Observations on Human Addicts During the Administration of Morphine, Arch. Int. Med. **43**:878 (June) 1929.

5. Light, Arthur B., and Torrance, Edward G.: Opium Addiction: II. Physical Characteristics and Physical Fitness of Addicts During the Administration of Morphine, Arch. Int. Med. **43**:326 (March) 1929.

climbing and Schneider's test showed a decrease in the efficiency of the circulation following the readministration of the drug when compared to the results obtained at the end of the forty-eight hour withdrawal period.[6]

Abrupt withdrawal of morphine in a series of human opium addicts resulted in a negative water balance, and in two of these subjects in increased elimination of uric acid. The negative water balance is most likely due to failure to take sufficient food and water although increased loss of water from increased metabolism cannot be entirely excluded, particularly in view of the restlessness of these subjects during withdrawal.

While taking their first year final examinations, three medical students used as control subjects failed to show a negative water balance, any increase in frequency of urination or increased twenty-four hour output, and retained their weights, on the days of the final examinations.[7]

Studies of a series of opium addicts before and after treatment with scopolamine resulted in the following positive changes: loss of weight, slight rise in temperature, appearance of albuminuria, slight leukocytosis, slight concentration of the blood, a rise in the p_H of the blood, a rise in the lactic acid of the blood, a fall in the carbon dioxide capacity and a fall in the total number of points scored with Schneider's test of physical fitness.

No significant changes were found in a comparison of the pulse, respiration rates and blood pressure while the addict was reclining, heart measurements, electrocardiographic studies, staircase climbing tests, effect of atropine sulphate on the P-R interval, vital capacities, blood urea nitrogen, blood sugar, blood uric acid, blood cholesterol, whole blood chloride, serum calcium and phosphate, blood viscosity, sedimentation tests, basal metabolism, phenolsulphonphthalein tests, phenoltetrachlorphthalein test of liver function, icterus index, van den Bergh's tests and blood sugar response to epinephrine.

The few positive observations do not coincide with the general appearance and behavior of the addict. He may present some or all of the foregoing positive observations and yet appear and behave as though he were normal. On the other hand, he may give the appear-

6. Light, Arthur B., and Torrance, Edward G.: Opium Addiction: VI. The Effects of Abrupt Withdrawal Followed by Readministration of Morphine in Human Addicts, with Special Reference to the Composition of the Blood, the Circulation and the Metabolism, Arch. Int. Med. **44**:1 (July) 1929.

7. Light, Arthur B., and Torrance, Edward G. Opium Addiction: IX. Water Balance Studies During the Administration and Withdrawal of Morphine, Arch. Int. Med. **44**:693 (Nov.) 1929.

ance of one who is quite ill and yet not show any of the foregoing positive observations.[8]

The effect of intramuscular and intravenous administration of large doses of morphine was tested on five addicts, one of whom was at times accustomed to the intravenous administration of the drug, while the other four, accustomed to the hypodermatic method, volunteered as subjects for this study.

The intramuscular injection of morphine sulphate in dosages of three, four and six times the usual amounts given, and the intravenous injection of dosages six, seven and nine times the amounts usually given to the human opium addicts who acted as subjects resulted in insignificant changes in the pulse and respiration rates, electrocardiogram, chemical studies of the blood and the behavior of the addict.

The intravenous administration of 20 and 11 grains (1.3 and 0.715 Gm.) to two addicts following a forty-eight hour withdrawal period in fifty-six minutes and one hour and sixteen minutes, respectively, also failed to produce any significant physiologic changes or changes in behavior.

Analyses of the blood for morphine showed the presence of less than 1 mg. per twenty-five cubic centimeters of blood, indicating its rapid removal following the completion of the injection.[9]

In a series of addicts it has been possible to control reliably the morphine dosage, to vary this at will and to collect the excreta quantitatively.

Quantitative estimation of the elimination of morphine in the urine of human addicts showed a remarkable constancy in ratio to the amounts administered. Daily administration of 15 (0.972 Gm.), 30 (1.944 Gm.) and 60 grains (3.888 Gm.) resulted in an average percentage elimination of 8.7, 9.8 and 10.7, respectively. The length of addiction, quantities taken just prior to admission, age, weight and urine volume did not influence this rate.

Fecal excretion of morphine fell far below the urinary level, but was too variable to justify general conclusions.

Abrupt withdrawal of morphine resulted in a rapid fall in urinary excretion during the first four hours followed by a much lower and constant level for the next twenty-six hours.

The elimination of morphine in an addict suffering with lobar pneumonia, to whom a daily administration of 15 grains (0.972 Gm.) was

8. Light, Arthur B., and Torrance, Edward G.: Opium Addiction: VII. A Comprehensive Study of the Effects of the Scopolamine Treatment for Morphine Addiction, Arch. Int. Med. **44**:194 (Aug.) 1929.

9. Light, Arthur B., and Torrance, Edward G.: Opium Addiction: VIII. The Effects of Intramuscular and Intravenous Administration of Large Doses of Morphine to Human Addicts, Arch. Int. Med. **44**:376 (Sept.) 1929.

maintained throughout the illness and convalescence, showed the same level of excretion during the early part of the disease, following the crisis and during the convalescent period, but a rise in the period just before the crisis when the patient was critically ill. No unusual signs or symptoms appeared during the illness that could be attributed to the morphine.[10]

COMMENT

These results are of definite importance. The study shows that morphine addiction is not characterized by physical deterioration or impairment of physical fitness aside from the addiction per se. There is no evidence of change in the circulatory, hepatic, renal or endocrine functions. When it is considered that these subjects had been addicted for at least five years, some of them for as long as twenty years, these negative observations are highly significant. The study offers substantial grounds for the belief that were it possible to relieve the addict of his addiction complete rehabilitation could be expected.

The abrupt withdrawal of morphine was accompanied by only slight changes in the physiologic mechanisms studied, changes which afforded no adequate explanation of the withdrawal symptoms.

The readministration of morphine during the period of the withdrawal symptoms was not accompanied by return to normal of those few positive observations characteristic of the withdrawal period in spite of the apparent return of the addicts to a sense of well being. Schneider's test of physical fitness and the staircase climbing test indicated a poorer response than during the period of suffering.

Following treatment and just before discharge from the hospital, our studies again indicate few changes except that the average leukocyte count was still high, a slight concentration of the blood still persisted, a slight rise in the average for the p_H and lactic acid of the plasma and a decided fall in the efficiency tests were found. One cannot correlate these observations with the behavior of the patients.

The study appears to us to be conclusive with respect to the physiologic reactions of the addict which we investigated. It indicates, however, the necessity for a study of the addict from some new standpoint in order to reveal the factors which induce and maintain the state of addiction and which on abrupt withdrawal of the drug elicit the withdrawal symptoms.

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10. Fry, Edith G.; Light, Arthur B.; Torrance, Edward G., and Wolff, William A.: Opium Addiction: X. Excretion of Morphine by Human Addicts, Arch. Int. Med., this issue, p. 862.

BLOOD PRESSURE AND WEIGHT*

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The study of large groups of persons seems to establish a definite relationship between the weight of the body and the arterial blood pressure. Faber,[1] in his report of 1,000 approximately normal children between the ages of 4 and 16 years, showed a striking and corresponding rise in both systolic and diastolic blood pressure with a rise in body weight in each group. Since arteriosclerosis and other diseases which predispose to arterial hypertension may be excluded in these persons, the evidence of the relationship of body weight to blood pressure appears even more conclusive. That deviation from the normal body weight is associated with definite variation in blood pressure in otherwise normal persons is well demonstrated by Symonds.[2] His review of the results of 150,419 examinations for life insurance revealed steplike variations in the blood pressure between the various groups. There was a fall in both systolic and diastolic pressure in each group in which the subjects were below normal body weight, and a corresponding rise in blood pressure in each group made up of persons who were above normal body weight.

The significance of the type of body build as related to blood pressure is pointed out by Larimore.[3] His studies of factory workers, of whom 177 were males and 237 females, show that persons of the sthenic type have definitely higher systolic and diastolic blood pressures than those who are of the asthenic type. In persons of the intermediary, hyposthenic type, the averages for blood pressure were between the averages for the sthenic and the asthenic groups. Faber [4] tended to corroborate this observation in his conclusion that in men of equal weight the blood pressure is slightly lower in those of greater height.

* Submitted for publication, May 28, 1929.

*From the Medical Division of the Mayo Clinic and the Mayo Foundation.

1. Faber, H. K.: A Formula Expressing a General Relationship Between Pressure and Body Weight, Proc. Soc. Exper. Biol. & Med. **25**:77, 1927.

2. Symonds, Brandreth: The Blood Pressure of Healthy Men and Women, J. A. M. A. **80**:232 (Jan. 27) 1923.

3. Larimore, J. W.: A Study of Blood Pressure in Relation to Types of Bodily Habitus, Arch. Int. Med. **31**:567 (April) 1923.

4. Faber, quoted by McWilliam, J. A.: Blood Pressure in Man, Normal and Pathological, Physiol. Rev. **5**:303, 1925.

The relation between arterial hypertension and groups of persons above normal body weight is pointed out by Huber,[5] who cited evidence obtained from the examination, in 1923, of 12,000 army officers. Furthermore, in his own study of the results of 1,332 examinations made in the army, he found that 18 per cent of those who were overweight had arterial hypertension (systolic); only 15 per cent of those of normal weight and 11 per cent of those who were underweight exhibited arterial hypertension (systolic). More striking evidence of this relationship is reported by Terry,[6] in whose series of sixty-three obese patients, thirty-seven (58 per cent) were found to have arterial hypertension, or average blood pressures of 173 systolic and 96 diastolic for the entire hypertensive group. Twenty-four of these obese patients were placed on a dietary regimen, and after an average loss of 12 pounds (5.4 Kg.), the average arterial blood pressure for the group of twenty-four fell from 196 systolic and 103 diastolic to 170 systolic and 95 diastolic. Similar results were reported by Rose[7] in his series of ten obese patients whose weights were reduced by a dietary regimen.

It has been shown[8] that in patients suffering from cholecystitis the blood pressure curve, when corrected for body weight, was lowered so that it varied little from the accepted curve for normal blood pressure and so that it correlated with that of patients with gastric ulcer. Moreover, the blood pressure curve in gastric ulcer was raised when a correction for weight was made. Since the body weight in cholecystitis frequently is above normal and that in gastric ulcer frequently is below normal, the value of correcting blood pressure for body weight seems evident.

PRESENT STUDY

A study has been undertaken for the purpose of determining the relationship, if any, that exists between arterial blood pressure and body weight. In other words, an attempt has been made to determine whether the rule that blood pressure is increased in obese and lowered in emaciated persons holds in the physician's office, irrespective of the medical status of his patients. The attempt was not to establish normal values, but to find whether impressions gained from normal persons apply to all patients in a general clinical practice, and to determine how dominant

5. Huber, E. G.: Systolic Blood Pressure of Healthy Adults in Relation to Body Weight, J. A. M. A. **88**:1554 (May 14) 1927.

6. Terry, A. H., Jr.: Obesity and Hypertension, J. A. M. A. **81**:1283 (Oct. 13) 1923.

7. Rose, R. H.: Weight Reduction and Its Remarkable Effect on High Blood Pressure, New York M. J. **115**:752, 1922.

8. Hartman, H. R., and Brown, G. E.: A Statistical Study of the Systolic Blood Pressure in Cases of Duodenal and Gastric Ulcer, this issue, p. 843.

is the factor of weight in influencing blood pressure. Many of the persons studied were in a normal state of health.

To obtain the data for this study, records of 2,042 consecutive registrants, aged 15 or more, were taken from the file of the Mayo Clinic for June, 1927. Nine hundred and fifty-nine of the subjects were males and 1,083 females.

By use of the Nylic Standard Table of Heights and Weights compiled by Dr. Oscar H. Rogers of the New York Life Insurance Company, percentage deviation from normal weight was computed in each case. Arrangement of groups by percentage deviation from normal was then accomplished for males and for females. Those persons within 10 per cent above or below the accepted normal were grouped as "normal." The grouping utilized was as follows:

Group 1.—26 to 50 per cent underweight
Group 2.—11 to 25 per cent underweight
Group 3.—Normal weight
Group 4.—11 to 25 per cent overweight
Group 5.—26 to 50 per cent overweight
Group 6.—51 to 75 per cent overweight
Total underweight
Total overweight

The mean blood pressures within each group subsequently were utilized to compute the systolic and diastolic blood pressures for each designated group. The probable errors of the differences were computed [9] to ascertain the significance of the variation between the blood pressures of the groups.

The average blood pressures for the groups, with the designation of the probable error, were then plotted graphically (charts 1 and 2). The minus probable error is shown in the charts.

COMMENT

Chart 1 shows in males an almost steplike rise from group 1 to group 6 in the mean values for the systolic blood pressures of the groups. Here the most significant rise of systolic blood pressure is demonstrable between groups 3 and 4. The marked difference between the total underweight (125.1 systolic) and the total overweight (141.2 systolic) male groups is strikingly significant, with odds of sixty-five billion to one given to this difference.[10]

9. Rugg, H. O.: Statistical Methods Applied to Education, Boston, Houghton Mifflin Company, 1917, pp. 410.

10. Pearl, Raymond: Medical Biometry and Statistics, Philadelphia, W. B. Saunders Company, 1923, p. 209.

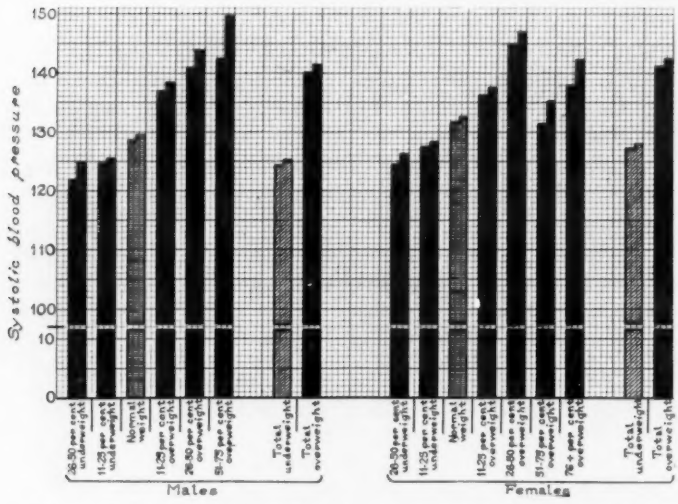

Chart 1.—Graphic representation of average systolic blood pressure in underweight and in overweight males and females, all ages. The plotted length of notches indicates the probable error. The horizontal white strip in this and the following chart indicates that the plot of blood pressure from 10 to 100 is omitted to save space.

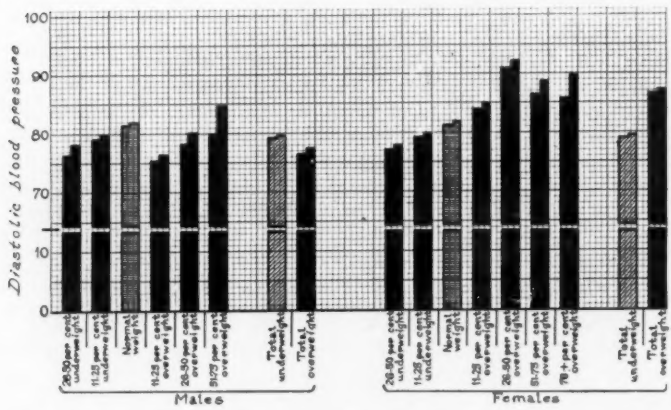

Chart 2.—Graphic representation of average diastolic blood pressure in underweight and in overweight males and females, all ages.

In the females there is a similar steplike rise in the systolic blood pressure, with increase in body weight until groups 5 and 6 are reached, where there is a fall from the peak (146.7 systolic). The small number of cases (eighteen and four, respectively) in these last groups allows this apparent discrepancy, but there is little or no significance in view of the large probable errors involved. The marked difference between the total underweight (127.8 systolic) and total overweight (142.2 systolic) female groups is practically as striking and is equally as significant as it is in the males.

In chart 2 it is shown that the means for diastolic pressures and the body weight were correlated in females only, and the differences between the classes according to weight, of course, were small. In the males the mean value for diastolic blood pressure in the total overweight group was even smaller than that in the total underweight group, and the means in the different groups according to weight were not consistent with the corresponding systolic averages. The small weight of significance given these diastolic variations allows for a possibility that a larger group study might reveal the expected steplike rise in males, as is found more significantly in females. The averages for diastolic pressure in the female group proved consistent with the corresponding systolic averages throughout.

This lack of constancy in diastolic blood pressure could be traced readily to lack of uniformity of technic in taking the readings. The phenomena on which the record of diastolic blood pressure is based are not as sharply defined as are those of the systolic pressure. All readings were taken by a trained but diversified group of clinicians who used a spring sphygmomanometer which every seven days was checked against a mercury sphygmomanometer. The inconstancy of the diastolic readings emphasizes only the striking constancy of increase of systolic blood pressure with increasing weight in a nonselected group of office patients in a general clinical practice. Weight must be a dominant factor in determining systolic blood pressure. Lack of correlation in the males, lack of uniformity of technic and instability of diastolic blood pressure itself preclude logical relationship being drawn between diastolic blood pressure and body weight in this particular study.

HEMOCHROMATOSIS IN A METAL WORKER

CASE REPORT WITH AUTOPSY AND A BRIEF REVIEW OF THE LITERATURE *

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The classic picture of "diabète bronzé" is rarely seen in this clinic, in spite of the belief of Mallory [1] that its fundamental pathologic background is not uncommon. Our interest was keen, therefore, when a man was admitted to the ward, not only presenting this condition in characteristic form, but also giving the remarkably apropos history that he had been a metal worker, in brass, steel and copper, for more than twenty years.

With the diagnosis practically "ready made" at the outset, we were able to plan and carry out fairly complete clinical and laboratory studies, which, together with autopsy observations, form the basis of this report.

Our purpose was: (1) to search for evidence of copper poisoning in relation to hemochromatosis; (2) to observe the effectiveness or non-effectiveness of insulin in controlling carbohydrate disturbances in a pancreatic disease known to be progressive and further complicated by liver disease, and (3) to study by clinical and laboratory methods the other endocrine glands which might be affected in this remarkable condition. When death ensued in spite of our best efforts, the autopsy enabled us to correlate the clinical and pathologic observations.

REPORT OF CASE

History.—J. M., a white man, aged 48, married, was admitted to the University of Pennsylvania Hospital to the service of Dr. Alfred Stengel on Dec. 21, 1927. Two years previously when he was apparently well he began to experience gnawing epigastric pain, three hours after meals, which was relieved by food and sodium bicarbonate. He had never been free from this pain for more than a week since its onset. About a year before, his friends noticed that the skin of his hands, forearms and face was becoming darker. This coloring progressed gradually until

* Submitted for publication, June 20, 1929.

* From the Medical Division Hospital of the University of Pennsylvania.

1. Mallory, F. B.; Parker, F., Jr., and Nye, R. N.: Experimental Pigment Cirrhosis Due to Copper, and Its Relation to Hemochromatosis, J. M. Research **42**:461, 1921. Mallory, F. B.: Hemochromatosis and Chronic Poisoning with Copper, Arch. Int. Med. **37**:336 (March) 1926; Relation of Chronic Poisoning with Copper to Hemochromatosis, Am. J. Path. **1**:117, 1925.

his admission to the hospital. About two months before admission he began to exhibit loss of weight, polydipsia and polyuria. Sugar was found in the urine at this time, although two previous examinations during the past year had been negative in this respect. He had blurring of vision, dyspnea and palpitation on exertion, weakness, loss of libido and some numbness and tingling of the finger-tips for the past two months.

He had had an umbilical hernia for two years, small hemorrhoids for ten years and multiple subcutaneous tumors for twenty years. He said that he had never had venereal disease.

His family history indicated nothing of importance except that he had four healthy children, and that his mother had similar multiple tumors beneath the skin.

He had worked in a machine shop for twenty years, usually with steel, often with brass and rarely with copper. During the grinding of these metals, he would become covered with the dust produced which would "work into his clothes," so that his underwear was thoroughly impregnated with it. He gave up this work three months before admission. His alcoholic habits were temperate. He took no silver preparations in any form.

Physical Examination.—On admission to the hospital, the temperature and pulse rate were normal; the blood pressure was 112 systolic and 68 diastolic. He was emaciated. The skin of the hands, forearms, face and neck was dry, scaly and of a striking dusky leaden hue. This pigmentation was less noticeable in those parts of the body covered by clothing. His face was feminine in configuration, with "retrousse" nose and pointed chin. His voice was feminine in tone. He had no axillary or thoracic hair, and the pubic hair was scanty and feminine in distribution. The mouth showed poor dental hygiene but no abnormal mucosal pigmentations. The heart and lungs were normal. Abdominal examination revealed a small umbilical hernia and a large, hard, bulging liver, extending down to within 1 cm. of the umbilicus. This organ showed relatively more enlargement of the left than of the right lobe so that its edge made a nearly horizontal line across the abdomen. The spleen was indefinitely palpable. On ausculation a peculiar humming sound was heard to the left of the umbilicus, not unlike the sound of wind blowing through telephone wires. It grew louder during cardiac systole and faded in diastole. It ceased entirely when moderately firm pressure was made with the stethoscope, or with the finger in the vicinity of the stethoscope. There was moderate ascites. The genitalia were grossly normal. There was general adenopathy of a mild degree. The multiple subcutaneous, circumscribed, fairly soft, almost symmetrical tumors, not more than fifteen in all, previously mentioned, were noticed in the various parts of the body, but chiefly on the extremities.

The diagnosis of hemochromatosis was made on the basis of this classic picture: a man in midlife with hepatic cirrhosis, diabetes mellitus and pigmentation. An additional unrelated diagnosis of familial lipomatosis completed our view of the case at this time. Abdominal neoplasm and Addison's disease were considered, but were ruled out.

Laboratory Studies.—The urine throughout showed sugar. Ketone bodies were present on admission, and appeared now and then during his stay in the hospital. There were neither casts nor albumin. Urobilin was strongly positive, and there was a trace of bilirubin at times. Rous' modification of the Perl test[2] for hemosiderin in the urine was negative on three occasions, except for the finding of a few blue extracellular particles. No hemosiderin granules were found in the

2. Rous, P.: Urinary Siderosis, J. Exper. Med. **28**:645, 1918.

unstained sediment. The intake and output of fluid bore normal relations to each other, except when ascites began to increase.

On admission, the blood showed a normal red and white cell count; hemoglobin, 82 per cent; and a differential count of neutrophils, 70; lymphocytes, 22; large mononuclears and transitionals, 8. Toward the end a moderate secondary anemia developed. No peculiarities were noted in the (Wright's) stained smear, and malarial organisms were not found. No phagocytes were seen containing hemosiderin. The reticulated red blood cells were 0.8 per cent. The fragility test was normal; hemolysis began at 0.450 and was complete at 0.325 per cent. The bleeding time was three minutes, and the tourniquet test was negative. The venous clotting time, clot retraction and blood fibrinogen were normal. The blood sugar varied from 0.145 to 0.280 per cent despite large doses of insulin daily (175 units) and a diet of protein, 75 Gm.; fat, 125 Gm., and carbohydrate, 100 Gm. The blood carbon dioxide in mild acidosis was 42 per cent by volume and rose to 62 per cent by volume subsequently. The Wassermann reaction of the blood was negative. The van den Bergh test showed an indirect reaction of 1.3 and a negative direct reaction. The icterus index was unobtainable because of hemolysis which occurred on each of three occasions. The blood urea nitrogen was 9, 5, 8 and 12 mg. per hundred cubic centimeters on various occasions.

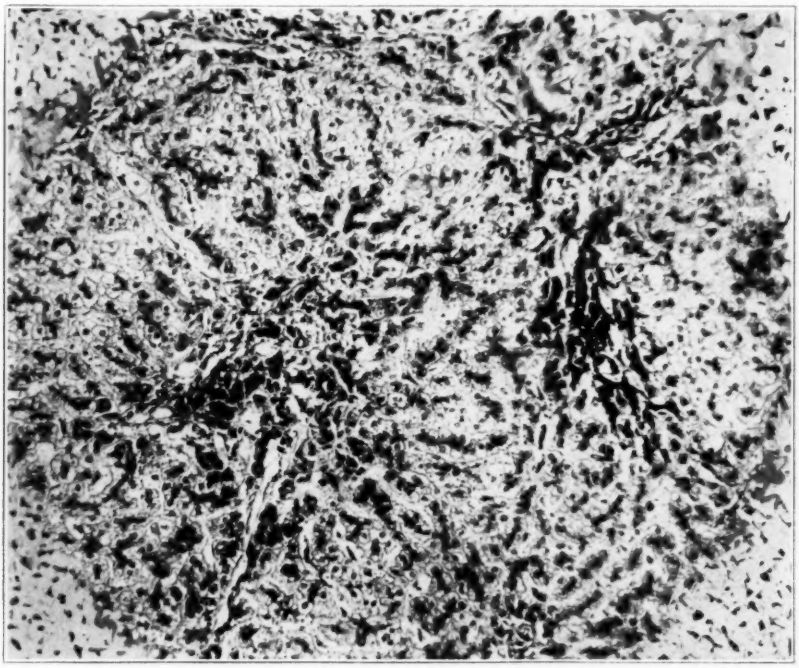

Fig. 1.—Section of the liver. Stained by Mallory's method (alum hematoxylin and ammonium sulphide). The hemosiderin granules take on an intense black color.

The ascitic fluid, obtained several times by paracentesis abdominis, was yellowish with a slight turbidity. The specific gravity was 1.008. There were 500 red and 52 white blood cells per cubic millimeter. Urea nitrogen and sugar were found in the same amounts that were present in the blood.

The basal metabolic rate was plus 2 per cent. Gastric analysis showed sustained high figures, the free hydrochloric acid being 72, the total hydrochloric acid, 88.

Roentgen studies gave the following results: The chest was normal. The pituitary fossa was slightly under the normal limits of size. Cholecystograms showed no shadow of the gallbladder in any of the films. Films of the gastro-

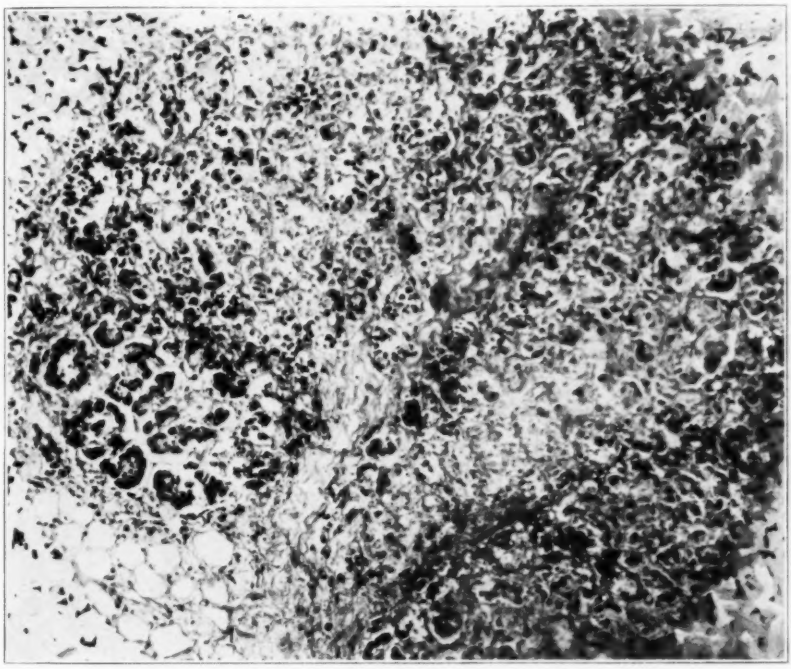

Fig. 2.—Section of the pancreas. Same stain as in figure 1.

intestinal tract showed hyperperistalsis and hypermotility in the stomach, a constant duodenal cap deformity by the fluoroscope but not in the serial films, phrenopasm in the esophagus and hypermotility in the colon.

The visual fields and eyegrounds presented nothing of importance. The electrocardiographic report was "rate 80, no arrhythmia recorded, P waves normal, P-R intervals 0.14 second, QRS complexes within normal limits, T-waves small in lead 1, inverted in lead 2. Tracing indicates marked functional depression of the myocardium, probably with myocardial disease."

A biopsy of the skin and of a lymph gland showed the presence of hemosiderin in considerable amounts in each. No copper was demonstrable. The subcutaneous tumors mentioned proved to be lipomas.

Course.—The subsequent course was a steadily downward one characterized by persistently high blood sugar, recurrent ascites, progressive emaciation, diarrhea, abdominal pain, weakness, moderate anemia and edema of the lower extremities. The increased blood sugar did not yield to massive doses of insulin. On 175 units per day and a diet of protein, 75 Gm., fat, 120 Gm., and carbohydrate, 100 Gm.; the blood sugar stayed consistently in the vicinity of 0.2 per cent. Increasing the insulin had little, if any, effect. Moreover, the patient showed evidence of insulin shock in only one rather doubtful instance.

Ten days after the last paracentesis abdominis, signs of peritonitis developed. This was attributed to a retrograde infection through the puncture wound, which

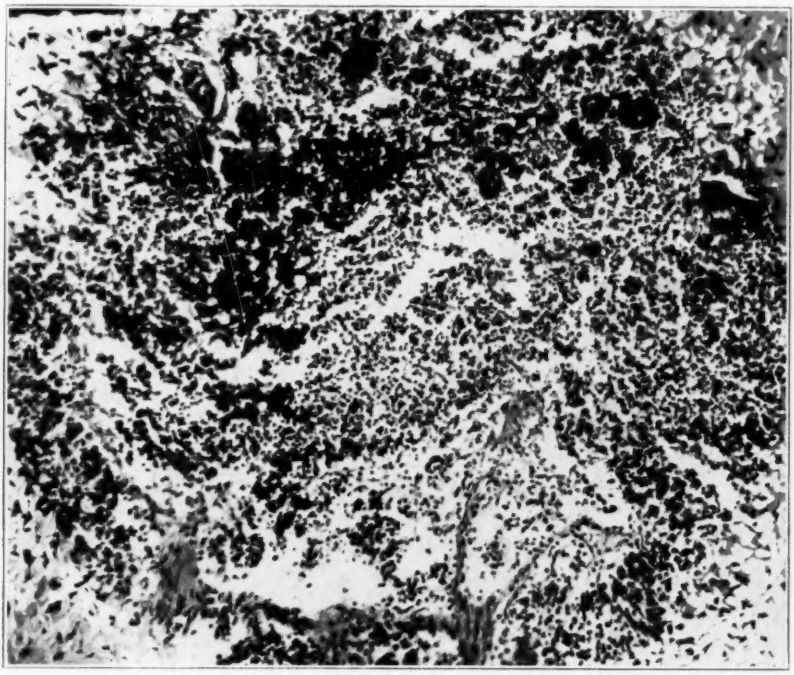

Fig. 3.—Section of a lymph node, near the pancreas. Same stain as in figure. 1.

had continued to drain for several days. The patient had neither fever nor leukocytosis at any time. He died, in coma, of peritonitis on Jan. 26, 1928, thirty-seven days after admission.

Autopsy.—At autopsy the typical observations of hemochromatosis[3] were present: cirrhosis and marked hemosiderin pigmentation of the liver (fig. 1); marked hemosiderosis of the pancreas (fig. 2), the color being a deep chocolate brown, and a considerable hemosiderin deposit in the heart muscle and lymph

3. Blanton, W. B., and Healy, W.: Hemachromatosis: Report of Four Cases, Arch. Int. Med. **27**:406 (April) 1921.

glands, especially those in the retroperitoneal chains near the liver and pancreas (fig. 3). No cause was found for the peculiar humming murmur to the left of the umbilicus, which was doubtless a venous bruit in the abdominal wall itself.

The immediate cause of death was a condition which should have been diagnosed from the history and gastro-intestinal studies, namely, a ruptured duodenal ulcer. The patient's typical history of ulcer was not appreciated correctly on account of the other upper abdominal pathologic changes. When the signs and symptoms of

Fig. 4.—Photograph of the patient taken on Dec. *27*, 1928. The pigment is most noticeable on the face, forearms, hands, legs and feet.

peritonitis developed, they followed uncomfortably closely on a paracentesis abdominis, so that the possibility of a ruptured ulcer was never suspected.

COMMENT

Hemochromatosis is a disease characterized by: (1) cirrhosis of the liver, (2) diabetes and (3) marked hemosiderin and hemofuscin deposits

in the various tissues, especially in the liver, pancreas, abdominal lymph nodes, exposed areas of the skin, heart muscle and endocrine glands. Hanot and Chauffard [4] the earliest writers, believed that diabetes produced a generalized perversion of cellular metabolism. The hepatic changes incident to this widespread metabolic derangement resulted in interference with chromogenic function, and this in turn caused the pigment deposits. Von Recklinghausen [5] considered hemochromatosis as a "chronic form of hemorrhagic hepatitis" and a sign of a hemorrhagic diathesis. Rendu and de Massary [6] and Brault and Galliard [7] suggested that the cirrhosis of the liver was probably the primary etiologic factor. According to their opinion, pigment was deposited as a result of the extreme cachexia caused by the combination of diabetes and cirrhosis of the liver. Letulle,[8] P. Marie [9] and Jeanselme [10] believed that the pigment deposits came first, and that pancreatic and hepatic changes were secondary to it. They ascribed the hemosiderosis to an excessive blood destruction by some unknown toxin. Opie,[11] in 1899, likewise thought that the hemosiderin deposit preceded and caused the cirrhosis and the diabetes, but found no evidence of blood destruction or regeneration. He therefore suggested that some underlying hepatic dysfunction, with inability of the liver cells to effect the normal elaboration of bile pigments from the hemoglobin of the blood, might be responsible for the accumulation of hemosiderin in the tissues. Sprunt [12] agreed that pigment deposits appeared first, but invoked an intracellular metabolic

4. Hanot and Chauffard: Cirrhose hypertrophique pigmentaire dans le diabète sucré, Rev. de méd. **2**:385, 1882.

5. Von Recklinghausen: Ueber Haemochromatose, Tageblatt der 62te Versammlung deutscher Naturforscher und Aertze in Heidelberg, 1889, p. 324.

6. Rendu and de Massary: Cirrhose et diabète bronzé, Bull. et mém. Soc. méd. d. hôp. de Paris **14**:163, 1897.

7. Brault, A., and Galliard, L.: Sur un cas de cirrhose hypertrophique pigmentaire dans le diabète sucré, Arch. gén. de méd. **1**:38, 1888.

8. Letulle: Cirrhose pigmentaire du foie, chez les diabetiques, Semaine méd. **5**:408, 1885.

9. Marie, P.: Sur un cas de diabète bronzé suivi d'autopsie, Semaine méd. **15**:229, 1895.

10. Jeanselme, M. E.: Hématologie et pathogénie du diabète bronzé, Bull. et mém. Soc. méd. de hôp. d. Paris **14**:179, 1897.

11. Opie, E. L.: A Case of Hemochromatosis: The Relation of Hemochromatosis: The Relation of Hemochromatosis to Bronzed Diabetes, J. Exper. Med. **4**:279, 1899.

12. Sprunt, T. P.: Hemochromatosis: A Report of Three Cases and a Discussion of the Pathologenesis, Arch. Int. Med. **8**:75 (July) 1911. Sprunt, T. P.; Colwell, H. S., and Hagen, H. J.: Pigment Formation in the Liver During Autolysis and Its Relation to the Pigmentation of Hemochromatosis, J. Exper. Med. **16**:607, 1912.

disorder of unknown origin as the cause of this separation of the "chromogenic groups of the proteid molecule" from the rest of the cell constituents.

Gaskell and his co-workers,[13] McClure [14] and Howard and Stevens [15] studied cases of hemochromatosis with reference to undue retention of iron, but their work, although careful, was largely inconclusive. Other workers [16] had had similar experiences. Rous and his co-workers,[17] by repeated transfusions in rabbits, showed that hemosiderin deposits, simulating those in hemochromatosis, could be produced by the ensuing increased blood destruction. They admitted, however, that such an excess of hemolysis could not be the sole cause of the disease. Rous believed that cirrhosis of the liver and pancreas due to some unknown toxin was probably primary and prior to pigment deposition.

Mallory [1] produced some interesting recent work on the etiology of hemochromatosis. His conclusions were that the disease is due to interference with the elimination of iron. He pointed out that normally from one twelfth to one twentieth of the total number of red blood cells are destroyed daily, and that failure to excrete the normal amount of iron would result in a marked accumulation of iron-containing products in the body. He considered the mechanism of this interference as probably due to chronic copper poisoning, in which the hemoglobin unites with copper to form cuprohemol. This substance is deposited in the tissues. The hemoglobin is then separated from the copper, and is changed to hemofuscin, an iron-containing compound with the iron bound in such a chemical fashion that it is incapable of reacting chemically to give the usual iron tests. By further action of the tissue enzymes the hemofuscin is changed to hemosiderin. These two substances act as foreign bodies and cause necrosis of the cells in which they lodge. Fibrosis follows, which produces dysfunction of the organs concerned. Mallory described hemofuscin and hemosiderin deposits in experimental animals as a result of poisoning them with small doses of copper over

13. Gaskell, J. F.; Sladden, A. F.; Mackenzie Wallis, R. L.; Vaile, P. L., and Garrod, A. E.: A Contribution to the Study of Bronzed Diabetes, Quart. J. Med. **2**:129, 1914.

14. McClure, C. W.: Metabolism in a Case of Hemochromatosis, Arch. Int. Med. **22**:610 (Nov.) 1918.

15. Howard, C. P., and Stevens, F. A.: The Iron Metabolism of Hemochromatosis, Arch. Int. Med. **20**:896 (Dec.) 1917.

16. Sheldon, J. H.: The Iron Content of the Tissues in Hemochromatosis with Special Reference to the Brain, Quart. J. Med. **21**:123, 1927. Dunn, J. S.: Discussion of Hemochromatosis, Brit. M. J. **2**:783, 1921. Telling, W. H. M.: Discussion of Hemochromatosis, Brit. M. J. **2**:784, 1921. Stewart, M. J.: The Cirrhosis of Hemochromatosis, Brit. M. J. **2**:1066, 1922.

17. Rous, P., and Oliver, J.: Experimental Hemochromatosis, J. Exper. Med. **28**:629, 1918.

long periods. He maintained that hemofuscin is deposited first and then changed to hemosiderin. This differs from the usual opinion. He showed the possible sources of human copper poisoning to be manifold: home brewed and distilled liquors, canned green vegetables colored with copper compounds and foods prepared in copper utensils in the presence of acids.

On inquiring into the histories of his patients, he found that some of them had worked with copper in machine shops for prolonged periods. He admitted that many patients present no such history, and that many copper workers do not contract the disease. However, the numerous, hitherto unrecognized sources of copper poisoning, and the marked differences in individual susceptibility to this substance, are considered by Mallory to be sufficient reason for these observations.

Hall and Butt [18] have obtained results similar to those of Mallory, but recently Flinn and von Glahn [19] created considerable doubt as to the validity of the foregoing hypothesis. They reported a pigmentation, similar to that described by Mallory, which they reproduced in rabbits' livers by the feeding of substances not containing copper, such as carrots and sodium acetate. Moreover, some of their rabbits developed pigment deposition on a normal laboratory diet. These experimenters failed to confirm Mallory's results in other animals.

Further work on this subject will be necessary to establish the similarity or difference between the types of pigmentation described by Mallory,[1] Hall and Butt,[18] Rous [17] and Flinn and von Glahn [19] before any conclusions on this subject can be formulated.

The history of our patient's metal work fits in with Mallory's hypothesis. We failed to demonstrate excess copper in tissue removed at biopsy, or in the blood or urine of our patient, but this failure merely duplicates that noted by Mallory. He explained this as being due to the fact that copper is present in the tissues of these patients in close combination with hemofuscin, where it cannot be demonstrated microchemically. As soon as the copper leaves this combination it is excreted. Sinclair,[20] in a case recently reported before the Association of American Physicians, discovered a greatly increased copper content in the liver, but his observation stands alone.

There remain a few isolated yet noteworthy points to be discussed.

In a paper entitled "Urinary Siderosis," [2] Rous described a test in which the urinary sediments of patients with hemochromatosis, when

18. Hall, E. M., and Butt, E. M.: Experimental Pigment Cirrhosis Due to Copper Poisoning: Its Relation to Hemochromatosis, Arch. Path. **6**:1 (July) 1928.

19. Flinn, F. B., and von Glahn, W. C.: A Chemical and Pathological Study of the Effects of Copper on the Liver, J. Exper. Med. **49**:5, 1929.

20. Sinclair, H.: Paper to be published.

examined fresh or when stained by his modification of the Perl method, were found to contain pathognomonic amounts of hemosiderin. His results were not confirmed on three examinations of the urine from our patient. The cause may have been an inexpertness in technic. It seems probable, however, that there may be hemosiderin in the urine of one patient and not in that of another, depending on the amount of pigmentation in the kidney. Rendu and de Massary [6] and Mallory found pigment scarce in the kidney. The cause was ascribed to the fact that tubule cells desquamate as soon as they are destroyed by the hemosiderin accumulation within them. According to Mallory's view, urinary siderosis would be more readily discoverable in a case in which the copper poisoning was recent and hemosiderin deposition active, than in an "old" case such as ours.

The association of duodenal ulcer with hepatic disease is a circumstance which is being considered as possibly more than mere chance, since Mann's [21] work on the etiology of peptic ulcer, and its production by reducing in amount, or by side-tracking, the hepatic and pancreatic secretions which normally enter the duodenum. Our study of the literature, however, failed to reveal any other case of hemochromatosis associated with peptic ulcer.

In a recent case reported by Allan and Constam,[22] the patient similarly died of a terminal peritonitis, but no duodenal ulcer was found at autopsy.

Althousen and Kerr,[23] reporting on this disease since the development of insulin, noted the peculiar nature of the insulin reactions. One of their cases showed extraordinary instability of the blood sugar level and a tendency to sudden hypoglycemic shock. This is the type of insulin response we expected to find in our patient, but evidently the liver disease was not so great as to destroy the reserve function of the hepatic glycogenesis and glycogenolysis. He was resistant to insulin, and his case was similar in this and some other respects to the recent case of Allan and Constam.[22] The mechanism of this resistance is discussed in this paper.

Hypotension, sexual impotence, changes in the basal metabolism and loss of body hair have been alluded to in case reports of this disease.[24]

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21. Mann, F. C.: Chemical and Mechanical Factors in Experimentally Produced Peptic Ulcer, Tr. A. Am. Phys. **42**:224, 1927.

22. Allan, F. N., and Constam, G. R.: Insulin Resistance in a Case of Bronze Diabetes, M. Clin. North America **12**:1677 (March) 1929.

23. Althousen, T. L., and Kerr, W. T.: Hemachromatosis; Report of Three Cases with a Result of Insulin Therapy in One Case, Endocrinology **11**:377, 1927.

24. Marsh, P. L.: Hemosiderosis: A Case of "Bronze Diabetes" with Endocrine Disturbances (Sexual Regression), Endocrinology **8**:795, 1924.

They are doubtless the results of endocrine injury (i.e., pigment cirrhosis), which is a frequent observation in hemochromatosis.[25] Our patient showed several of these changes.

The electrocardiogram accurately foretold the heart muscle damage found at autopsy.

The preponderating left-sided hepatic enlargement noted in this patient has been mentioned as being present in other cases.[26]

Three specimens of blood were sent to the laboratory for icterus index tests. The report on each specimen stated that hemolysis had caused discoloration of the serum sufficiently to preclude the performance of the test. Unfortunately, nothing was thought of this at that time, but it occurs to us that there might be some underlying factor, as yet not understood, which was responsible for this phenomenon on three separate occasions. We merely report it as suggestive and deserving of further study.

SUMMARY

A typical case of advanced hemochromatosis occurring in a metal worker is reported with detailed clinical, laboratory and autopsy observations. The literature is briefly reviewed, and the possible etiologic rôle of chronic copper poisoning is discussed. We feel that chronic copper poisoning has not yet been proved to be the cause of this disease.

25. Sprunt (footnote 12, first reference). Blanton and Healy (footnote 3).

26. Sprunt (footnote 12, first reference).

EXPERIMENTAL LEFT AND RIGHT AXIS DEVIATION *

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AND
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A method of placing and distending a balloon in various chambers of the heart and in the great vessels was previously described.[1] This method permits electrocardiographic observation of the effect of increased pressure within and distention of the cardiac cavities and of obstruction to blood flow in the great vessels of the intact young dog under light ether anesthesia.

This method of study has many undesirable features. It is difficult to state what degree of pressure is exerted on adjacent structures. With the baloon placed in the right ventricle, pressure might be exerted through the septum influencing the mitral or aortic orifices, or on the A-V node, His bundle, right bundle branch and its arborizations, or there could be interference with the flow of blood through the right ventricle by obstruction of the tricuspid orifice or of the entrance to the pulmonary artery orifice. Likewise with the balloon in the left ventricle pressure might be exerted through the septum onto the tricuspid and pulmonary artery orifices, on the A-V node, His bundle, left bundle branch and arborizations or on the mitral and aortic orifices. There are degrees of interference with the coronary circulation. The normal movements of the contracting heart may be prevented; e. g., the twisting of the heart on its own axis as it goes into systole. With the balloon in the great vessels it is not certain that they are completely occluded, especially on the arterial side. When possible, efforts were made in various ways to reduce to a minimum the influence of these complicating factors. Further work will be done observing arterial and venous blood pressure and rate of coronary flow. A small balloon was used to cause the least amount of pressure on adjacent structures. In the experiments on the left ventricle the right side of the heart was drained on both sides of the tricuspid valve in an attempt to obviate the influence of congestion within the pulmonary circulation and distention of the right side of the heart. Since a single electro-

* Submitted for publication, July 9, 1929.

* From the Department of Medicine of Rush Medical College, University of Chicago.

1. Lundy, C. J., and Woodruff, L. W.: Experimental Heart Block, Arch. Int. Med. **43**:184 (Feb.) 1929.

cardiograph was used, only one lead was properly standardized; the other was quickly thrown in and recorded without standardization. Since in this paper attention is paid chiefly to gross discordance of Q R S of leads I and III, it is felt that general conclusions are warranted.

There are some desirable features. The method is used on the intact dog. Complete recovery occurs. It is possible to influence separately either the right or the left ventricle. The experiments may be repeated many times on the same dog. It is desirable, however, to observe the position of the balloon at autopsy after each experiment.

RESULTS

The balloon was placed entirely within the right ventricle and its pressure raised, while observing lead I, until a change in the electrocardiogram was noticed when a short observation of lead III was made. The change usually occurred at a pressure between that of systole and diastole as determined in the dog with a sphygmomanometer cuff around the abdomen compressing the abdominal aorta. In the dogs used, systolic pressure varied from 120 to 300 plus mm. of mercury, and the diastolic pressure varied from 50 to 210 mm. of mercury. On raising the pressure within the right ventricle Q R S_1 gradually became inverted, while Q R S_3 remained upright (fig. 1). Immediately on release of the pressure Q R S_1 gradually returned to upright, while Q R S_3 remained upright. Repetition of the experiment on the same dog, lead III being used with frequent observations of lead I, showed Q R S_3 increase slightly in height while Q R S_1 had become inverted; on release of the pressure Q R S_{1-3}, both rapidly returned to control form. These results produced a picture identical with that of right axis deviation.

Observations made with the balloon in the right auricle showed inversion of Q R S_1 late in the experiment after block had set in. With the balloon distending the tricuspid orifice (and seeming to vary with the simultaneous and proportionate distention of the right ventricle as compared with the right auricle), Q R S_{1-2-3} became inverted. The time of appearance of the inversion of Q R S in all leads varied in different dogs between immediately appearing without slowing of the rate or without the appearance of block up to the time of the appearance of what seemed to be right bundle branch block. At times the inversion of Q R S in all leads set in after complete block had occurred, yet without marked slowing of the rate, and finally it also appeared after marked slowing of the rate, and the dog was practically pulseless.

After the picture of right axis deviation with the balloon in the right ventricle had been produced, it was expected that a picture of left axis deviation might as easily be produced with the balloon distend-

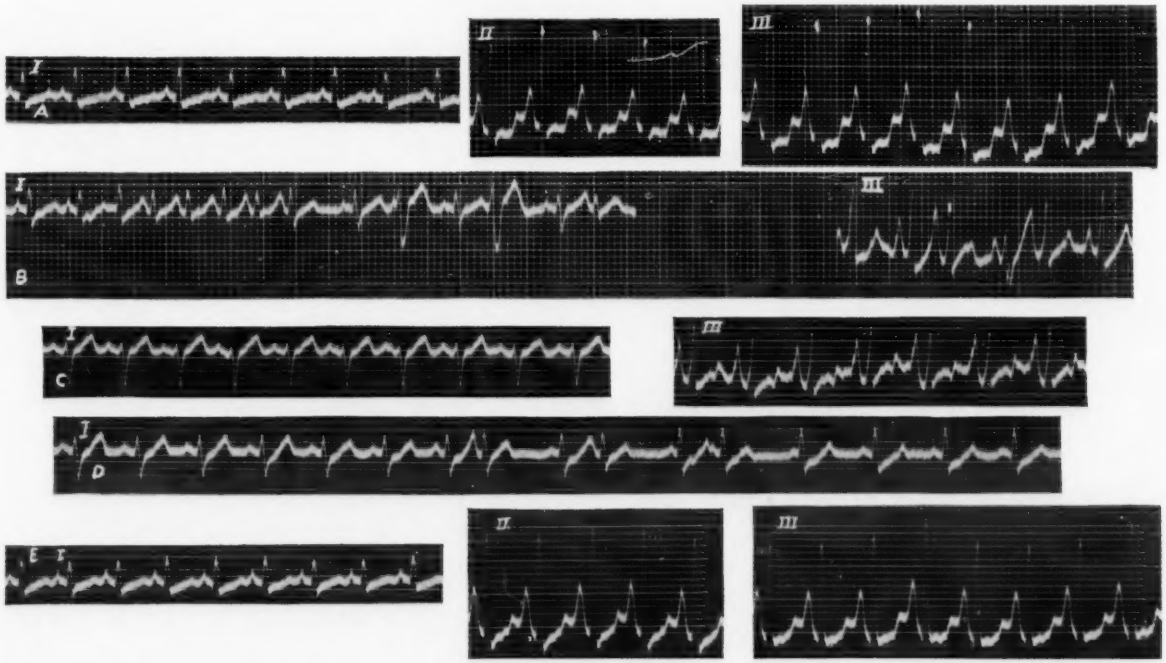

Fig. 1 (dog 49).—Balloon entirely within the right ventricle. At autopsy the right ventricle was found to be slightly dilated. *A* shows control after balloon was placed within the right ventricle. $R_2 = 1.3$ to 1.5 millivolts and $R_3 = 1.7$ to 1.5 millivolts. *B*, pressure of 200 mm. of mercury was applied. A gradual inversion of Q R S_1 with Q R S_3 remaining upright is shown. The extrasystoles should be noted. Lead III not standardized, 1 cm. > 1 mv. *C*, complete inversion of Q R S_1 occurred with Q R S_3 remaining upright. Lead III not standardized, 1 cm. > 1mv. *D*, immediately after pressure was released, showing gradual return of Q R S_1 to upright. The extrasystoles should be noted. *E*, control after five minutes, showing recovery. In all tracings the time intervals are of one-twenty-fifth second or 2.5 cm. equals 1 second. Standardization is 1 cm. equals 1 mv. except when otherwise specified. White dots indicate limits of excursions.

ing the left ventricle. This was not true, however, for an entirely different situation was encountered. A pressure higher than the systolic pressure of the dog was required. The balloons available would not always withstand such high pressure. When used, this high pressure often caused extrasystoles and even ventricular fibrillation, presumably because of embarrassment of the coronary circulation as well as of distention of the left ventricle. Moreover, it was usually impossible to raise the left intraventricular pressure without causing congestion of the pulmonary circulation and right side of the heart with distention of the right ventricle. This is due in part to the configuration of the left ventricular chamber on the septal side, which makes it rather easy to force the balloon against the aortic orifice and to obstruct the blood flow at that site. The long cone-shaped character of the right ventricular chamber as it extends to the orifice of the pulmonary artery, together with the lower intraventricular pressure, permits a continuation of the circulation through that side of the heart in spite of the presence of the balloon.

Attempts to overcome these difficulties were made by using a small balloon, and by inserting a cannula into the right ventricle, right auricle or superior vena cava and draining the right side of the heart about two seconds after the pressure was increased in the left ventricle. Observations showed (fig. 2) that on increasing the left intraventricular pressure, S_3 would appear if absent before, or if present before would become increased from 0.2 and 0.3 millivolt to 0.4 and 0.5 millivolt, while R_3 would diminish from 1.2 and 1.4 to 0.8 millivolt, R_1 would increase in height. The increased S_3 lasts for but a few seconds when the wave almost and at times entirely disappears, while R_1 and R_3 both become increased in height. When drainage from the right side of the heart was instituted, it was noted that S_3 would again increase, at times more than when pressure was applied without drainage, and R_3 would almost always show a corresponding diminution in height. R_1 was always increased in height under both circumstances. When drainage of the right side of the heart was instituted before the initial increase of S_3 disappeared, it would persist as long as the congestion of the right side of the heart was prevented. Even when S_3 had disappeared after its initial appearance or increase, drainage of the right side of the heart would cause it to reappear. In experiments with and without drainage it was observed that S_3 increased in height still further immediately after the increased left intraventricular pressure caused by the distended balloon was released, and this increase of S_3 would persist until most of the water had been expelled from the balloon and then Q R S_{1-3} would both rapidly return to control form. Drainage of the right side of the heart without pressure being applied within the left ventricle did not influence S_3 in this manner; such

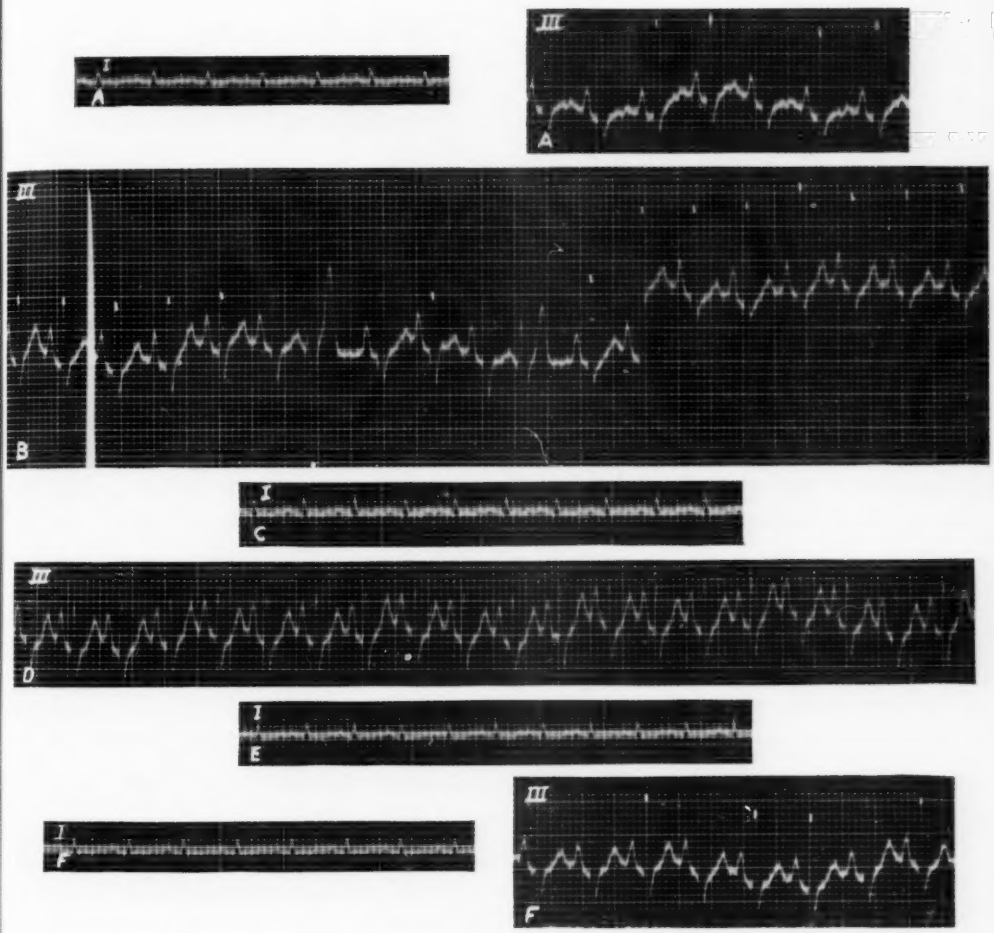

Fig. 2 (dog 68).—Balloon entirely within the left ventricle. *A* shows control with balloon in left ventricle and glass tube in right ventricle. $R_3 = 1.25$ to 1.35 millivolts; $S_3 = 0.25$ to 0.3 millivolts. *B*, pressure of 340 mm. was applied at mark. S_3 increases from 0.25 and 0.3 to 0.4 millivolts within three seconds, diminishing to 0.1 and 0.15 millivolts immediately after. R_3 diminishes from 1 to 0.8 millivolts and within three seconds increases to 1.6 millivolts. *C*, observation with pressure maintained shows R_1 increased to 0.2 plus mv. Lead I not standardized, 1 cm. $<$ 1 mv. *D*, during drainage of right side of heart with pressure maintained in the left ventricle. R_3 has diminished to 0.6 millivolt, while S_3 has again increased to 0.4 millivolt. *E*, observation during drainage of right side of heart. $R_1 = 0.15$ mv. Lead I not standardized, 1 cm. $<$ 1 mv. *F*, recovery after pressure released and drainage stopped. $R_1 = 0.15$ mv. $R_3 = 1.1$ to 1.2 and $S_3 = 0.3$ mv.

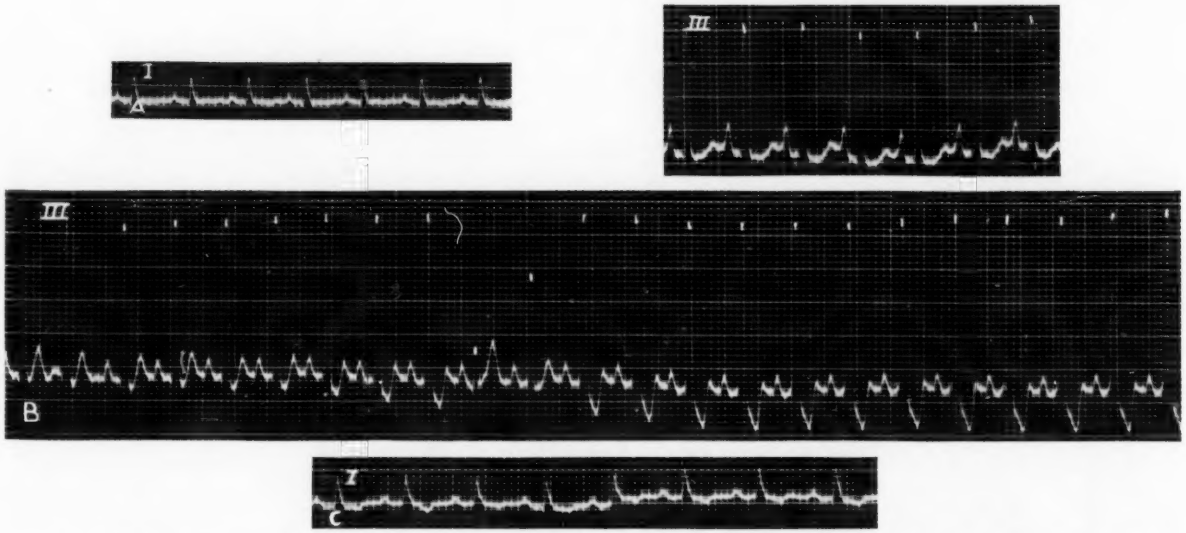

Fig. 3 (dog 52).—Balloon at aortic orifice, *A* shows control with balloon in aortic orifice. $R_1 = 0.38$ millivolt; $R_3 = 1.9$ millivolt. *B*, pressure suddenly raised to 440 mm. of mercury. R_3 increased from 1.9 and 2 mv. to 2.5 mv. Note T_3 inversion onset and extrasystole. *C*, control observation while pressure was maintained. R_1 as high as 0.42 millivolt. Lead I not standardized, 1 cm. $<$ 1 millivolt.

drainage could never be made at the same rate even when instituted under high negative pressure.

These results show evidence of increased activity of the left ventricle and while not so marked as in the experiments on the right ventricle, they seem to be outside the limits of error and might be considered as a picture of a tendency to left axis deviation.

Obstruction of the aorta at its orifice, or anywhere throughout its course, gave results similar to each other but no such evidence of increased activity of the left ventricle. In these experiments, Q R S_{1-3} both showed an increased height of R (fig. 3).

A definite picture of left axis deviation was produced by placing the balloon in the inferior vena cava midway between the hepatic vein and right auricle (fig. 4). On increasing the pressure sufficiently to obstruct the inferior vena cava, Q R S_3 gradually became completely inverted while Q R S_1 remained upright. Immediately on releasing the pressure, Q R S_{1-3} both returned to control form.

A fortunate accident enabled the production of a picture of left axis deviation in the intact dog by experimental pericardial effusion (fig. 5). The balloon, on being inserted into the right side of the heart, became broken, and the tip of the glass tubing pierced the right auricle at the base anteriorly. On injection of water into the pericardial sac up to a pressure of 90 mm. of mercury, Q R S_3 rather rapidly became completely inverted, whereas Q R S_1 remained upright but diminished in height. Release of the pressure caused prompt return to control form.

INTERPRETATION AND COMMENT

It seems advisable to attempt to explain why this apparently increased activity of one or the other ventricles of the heart is produced under the given conditions. Reflex action by way of the vagus has been ruled out. It should be needless to say that it was not due to hypertrophy because of insufficient time. It does not seem that it was produced by rotation of the heart on its own axis or by the heart as a whole being displaced to one side because the dogs were rotated to each side during the experiments, and this never caused the tracings to return to control form, nor was the glass tubing attached to the balloon seen to change its position except when the dogs themselves were rotated. With the balloon in the inferior vena cava it does not seem that there could be any disturbance of the position of the heart as a whole.

An interesting observation was made in two of the experiments on the right ventricle which might shed considerable light on the interpretation of the results in this entire group of experiments and in addition on the influence of cardiodynamic changes on heart action as well as on the interpretation of axis deviation. These observations

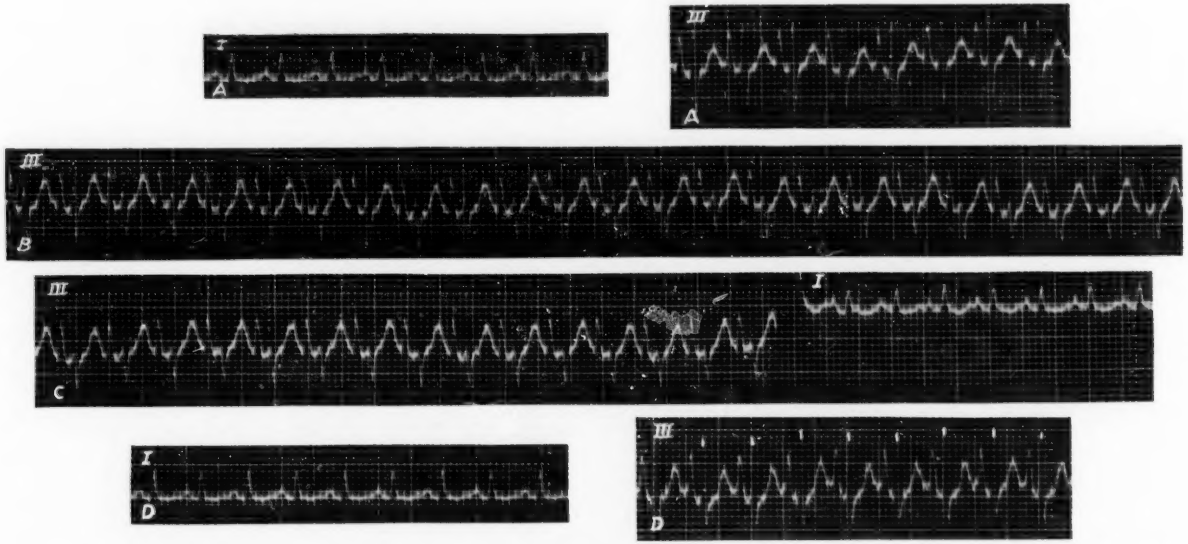

Fig. 4 (dog 73).—Obstruction of inferior cava. *A* shows control after balloon inserted into inferior vena cava. $R_1 = 0.3$ millivolt; $R_3 = 0.6$ millivolt and $S_3 = 0.5$ millivolt. *B*, pressure 200 mm. of mercury applied. Q R S_3 shows gradual inversion. $R_3 = 0.1$ millivolt and $S_3 = 0.45$ millivolt. *C*, shows complete inversion of Q R S_3 with Q R S_1 remaining upright. $R_3 = 0.05$ millivolt; $S_3 = 0.4$ millivolt and $R_1 = 0.3$ millivolt. Lead I not standardized, 1 cm. < 1 millivolt. *D*, control after pressure is released. $R_1 = 0.32$ millivolt; $R_3 = 0.9$ to 1 millivolt and $S_3 = 0.3$ millivolt.

are of special interest when considered in relation to the view of Eyster, Meek and Hodges [2] that dilation of the heart precedes hypertrophy. In these two experiments, right axis deviation was produced with the balloon in the right ventricle. Unlike the other experiments on the right ventricle, after release of the pressure, the tracings never returned to control form (fig. 6). Q R S_1 remained diphasic, giving a more or less permanent right axis deviation. All of the experiments

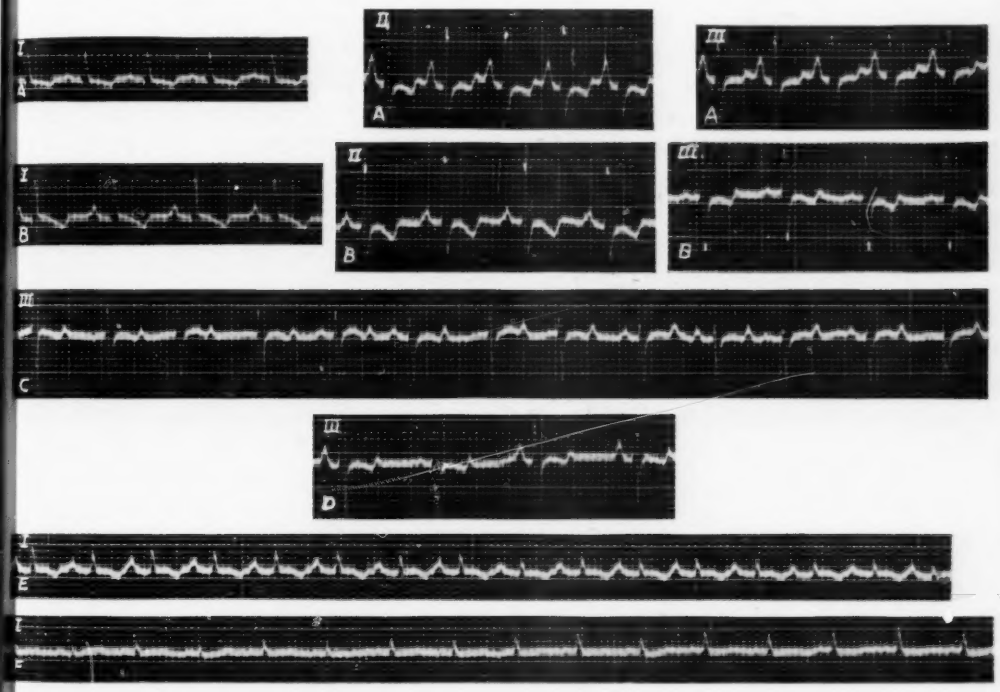

Fig. 5 (dog 7).—Experimental pericardial effusion. *A* shows control before tube was inserted. $R_1 = 0.4$ millivolt; $R_3 = 0.6$ millivolt and $S_3 = 0.5$ millivolt. *B*, control after tube was inserted and had perforated base of right auricle anteriorly. Note the notched $P_{1_2_3}$. $R_1 = 0.55$ millivolt; $R_3 = 0.6$ millivolt and $S_3 = 0.6$ millivolt. *C*, pressure of 90 mm. of mercury applied. Q R S_3 gradually becomes completely inverted. Note the diminished P_3. R_3 goes to 0.1 millivolt and S_3 goes to 0.7 millivolt. *D*, pressure released; Q R S_3 has returned to control form. *E*, pressure again increased to 60 mm. of mercury. Q R S_3 gradually diminishes in height but remains upright. *F*, pressure released. Q R S_3 gradually returns to control height. Note failure of P_3 to return to control height.

2. Eyster, J. A. E.; Meek, W. J., and Hodges, F. J.: Cardiac Changes Subsequent to Experimental Aortic Lesions, Arch. Int. Med. **39**: 536 (April) 1927.

reported were crucial, and observations were never made after four or five hours and were usually made within a few minutes. Q R S_1 might have returned to control form if sufficient time had been given for recovery. But something had caused these two experiments to

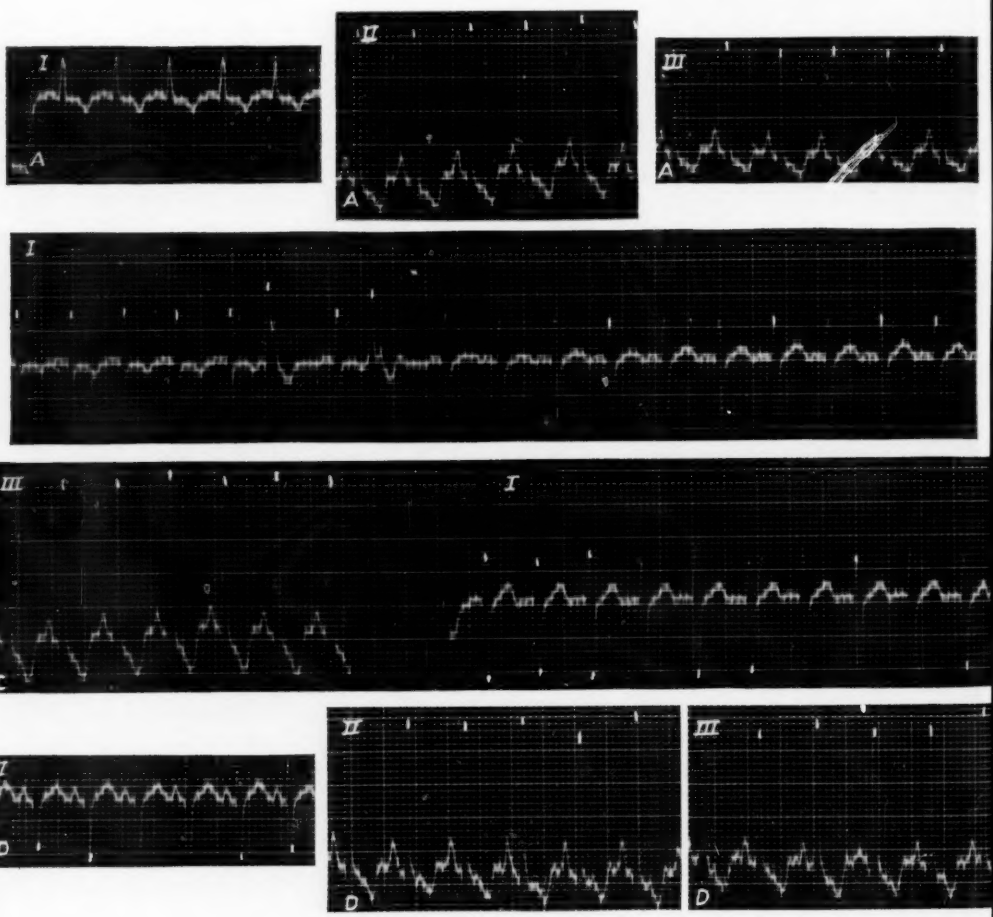

Fig. 6 (dog 42).—Balloon entirely within right ventricle. At autopsy the right ventricle was found to be greatly dilated. *A* shows control after balloon was inserted into the right ventricle. $R_1 = 0.55$ millivolt and $R_3 = 1.6$ millivolt. *B*, pressure of 240 mm. of mercury applied. Note the extrasystoles. Sudden appearance of deep S_3 with T_3 changing from inverted to upright. *C*, Q R S_3 remains upright. Q R S_1 as in *B*. Lead III not standardized, 1 cm. $>$ 1 millivolt. *D*, observation four hours later showing Q R S_1 remaining diphasic with Q R S_{2-3} upright.

show a change which was more permanent than any similar experiment. At autopsy it was found that the right ventricles were greatly dilated, more so than in any of the other experiments on the right ventricle. It should be mentioned that the right ventricle was found to be somewhat dilated in all of the experiments, but this may have been due to the heart dying with the right ventricle in diastole. The left ventricle was found slightly dilated only in the experiments on the left ventricle, and only once was it found slightly more dilated than usual with no unusual electrocardiographic observations in that experiment.

The marked dilation of the right ventricle alone associated with a more permanent right axis deviation leads to the consideration of the influence of stretching the heart on its action current. We are not yet prepared to say that stretching the ventricle in this manner injured the individual cell membranes or whatever condition exists that delimits cells from each other. Eyster [3] reported a condition of "hydropic degeneration" found in dogs with dilatation of the whole heart. Dubrow [4] reported fatty degeneration more pronounced in the right ventricles of dogs showing right axis deviation subsequent to pneumothorax. The stretching of the muscle of the right ventricle produced a change associated with electrocardiographic evidence of increased activity of only that part of the heart which was stretched. Whatever the nature of the change may be, in most instances it was temporary, while in these two experiments it was more permanent.

Bayliss [5] said, "Increased permeability runs parallel with increased excitability of muscle." It might be said that the nervous impulse acting on heart muscle injured in this manner produces an increased action current because the stretched heart muscle is in a state of increased excitability. Further, if the permeability of the cell membrane is increased, or if the interfacial surface tension between cells is influenced, the state of increased excitability could be due to increased conductivity between cells because of the more ready diffusion of ions or electrolytes through the changed cell membranes, or interfacial surfaces of the cells, thereby lowering the resistance between cells. The lowered resistance between the cells of itself would give a stronger current as registered in the electrocardiographic record. This is consistent with an unvarying impulse conforming to Ohm's Law; $\frac{\text{volts}}{\text{ohms}} = \text{amperes}$. With such an interpretation of the mechanism involved, it could be said that the picture of right axis

3. Eyster, J. A. E.: Cardiac Dilatation and Hypertrophy, Tr. A. Am. Phys. **42**:15, 1927.

4. Dubrow, J. L.: Effect of Permanent Pulmonary Collapse on the Heart, J. A. M. A. **90**:1364 (April 28) 1928.

5. Bayliss, W. M.: Principles of General Physiology, New York, Longmans, Green & Company, 1924, p. 398.

deviation was produced by stretching the right ventricle and thereby increasing its excitability. That this could be a matter of the degree of stretching of the heart muscle, permitting a more or less intimate contact between the electrolytes of the individual cells producing a proportionate degree of increased excitability, is a conjecture not without reason and evidence; for it was observed that when the right ventricle was moderately stretched, the right axis deviation rapidly returned to normal control form, whereas when the right ventricle was greatly stretched, it did not return to control form within four hours. In some experiments, for various reasons, we did not get so great a degree of axis deviation as in others. Similarly, the rate of propagation of the action current might be increased, as observed by shortened time of Q R S which usually returned to control length.

A fourth factor which could act in a similar manner might be due to the distended balloon partially obstructing the venous drainage of the heart and maybe only locally within the right ventricle. The partial asphyxia produced thereby might increase the permeability of the cell membrane, or it might influence the electrolytes of the cells making them more diffusible by changing their character or increasing their concentration. Factors operating in a different way could be: fifth, change in the direction of the action current associated with change in the direction of the muscle fibers; sixth, a change in the relative volume or mass ratio between the right and left ventricles which might result (*a*) because the right ventricle is distended and (*b*) because the left ventricle might be actually smaller, owing to a diminished amount of blood being supplied to it.

The results obtained with the balloon at the tricuspid orifice are difficult to interpret. These observations have not been adequately controlled. No consideration is given to those instances of inversion after complete block had occurred with a greatly slowed rate and a practically pulseless dog. One similar clinical observation showed a similar downward deflection of Q R S in all leads, but P_1 and T_1 also were inverted, leading to the diagnosis of congenital dextrocardia with left axis deviation. The x-ray picture showed the heart and liver transposed. The inversion of Q R S in all leads of this group of experiments appears confusing, except that there seems to be a relationship to the balloon being in the aortic orifice in which Q R S of all leads increases in height and is directed upward. It is possible that right and left bundle branch block was produced when the balloon distended respectively the tricuspid and aortic orifices.

The picture of left axis deviation produced by obstructing the blood flow in the inferior vena cava may be due to increased peripheral resistance which could cause stretching of the left ventricle and maybe

increased excitability in a manner similar to that of the experiments on the right ventricle except that the blood damming back is the stretching agent. Here, too, the right ventricle would not be normally distended owing to diminished return flow of blood to the right side of the heart. This would decrease its relative volume or mass ratio even to a normally distended left ventricle. Also, the right ventricle might have a decreased action current owing to decreased excitability on the basis of the mechanism already described. These several factors operating together would further increase the tendency to left axis deviation.

The picture of left axis deviation produced by the experimental pericardial effusion was probably largely due to the extracardiac pressure interfering with the normal distention of the right ventricle more than the left, producing to a certain degree a relative left axis deviation. The incomplete filling of the right ventricle should be reflected back through the general circulation, causing greater distention of the left ventricle and some actual left axis deviation. In this regard it is interesting to observe that P_{1-3} were suppressed along with inversion of Q R S_3 and suppression of R_1, and that they did not always return to control form because the extracardiac pressure could not be reduced sufficiently to permit normal filling of the auricles. However, a sinus rhythm was maintained throughout.

With the balloon in the aortic orifice and in all divisions of the aorta, R_{1-3} were both increased in height. It is felt that this was probably because the right and left ventricles were distended almost simultaneously, owing to rapid congestion in the pulmonary circulation.

A satisfactory picture of left axis deviation was not produced with the balloon in the left ventricle, probably because of marked interference with the coronary circulation. However, it is felt that evidence of a tendency to left axis deviation was produced, and that it was due to the reasons already given. In these experiments on the left ventricle the factor of partial asphyxia may be more pronounced.

Clinical observation of shifting of the electrical axis in phasic variation unrelated to the respiratory rate is not uncommon. We have observed such shifting with Q R S, varying from entirely upright to completely inverted. In this connection we wish to report that in most of the seventy-three dogs observed in these experiments, a similar but less marked shifting of the electrical axis was seen in all leads, and more frequently after the heart had been weakened by the experimental procedure. It was observed often during marked tachycardia. It should be said that we have seen many clinical electrocardiograms with tachycardia which do not show this shifting. We have seen it most often in hearts with some degree of myocardial damage. It

seems that this shifting could be due to the flux of blood resulting from an imbalance of blood pressure and blood volume between the two ventricles causing gradual waxing and waning of the power of contraction of the separate ventricles, which might be due to corresponding variations of distention of the separate ventricles.

The theory involved in these experiments is common knowledge of long standing. Heidenhain and Hering [6] explained the production of extrasystoles as being due to dilation of the ventricles following ligation of the abdominal aorta. Vaquez [7] definitely stated that he believes some extrasystoles are produced by "stretching" of the heart causing increased excitability. The value of these experiments lies in the fact that each one of three chambers of the heart can be stretched separately. This permits analysis of the results without the difficulty of interpreting the complicating influence of both sides of the heart being influenced almost simultaneously, as occurs on ligation of the aorta. We observed many extrasystoles on introduction of the balloon into the heart and when the pressure was being raised. Few were noticed while the pressure was maintained at a constant level, or when it was lowered.

Clinical application of the mechanism presented herewith for increasing the excitability of the heart as a whole or in part is made to some extrasystoles. It can readily be conceived that a heart damaged by local anemia would be weakened in that region. Similarly, a heart, while equally injured throughout by toxic substances, might be conceived to have the effect of this injury produce more damage in certain areas than in others, owing to local causes such as a thinner heart wall, e. g., at the apex and between the trabeculae carneae in the ventricles and between the muscle bands in the auricles. Such weakened areas would probably be stretched more than the rest of the heart during the stress and strain of its activity, with the possible resultant increased excitability of such areas. Such a view seems to be compatible with Mines' theory [8] of reentrant waves as a cause for some extrasystoles. If such an application to extrasystoles should prove to be of value in determining their cause, of course the application would extend especially to related arrhythmias. It should be unnecessary to state that caution, more experience and much deliberation will be required for a true evaluation of these experiments as giving evidence of the influence of cardiodynamics on the activity of the heart.

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6. Heidenhain and Hering, quoted by Vaquez, H.: Diseases of the Heart, Philadelphia, W. B. Saunders Company, 1924, p. 489.

7. Vaquez, Henri: Diseases of the Heart, Philadelphia, W. B. Saunders Company, 1924, p. 489.

8. Mines, G. R.: Dynamic Equilibrium in the Heart, J. Physiol. **46**:349, 1913.

SUMMARY

Factors operating in these experiments to produce electrocardiographic evidence of left or right axis deviation may be:

1. Stretching of the muscle cells of the individual ventricles produced directly by the balloon or distention with blood may cause increased permeability of the cell membranes, thereby increasing the excitability of that individual ventricle with corresponding electrocardiographic evidence of axis deviation.

2. The lowered resistance produced in this manner between the individual cells may account for a small part of the axis deviation.

3. Partial asphyxia may cause an increased permeability of the cell membranes or may change the character or concentration of the electrolytes contained within the cells making them more diffusible.

4. The rate of propagation of the action current may be increased.

5. There may be a change in the direction of the action current associated with a change in the direction of the nerve fibers caused by distention with the balloon.

6. There may be a change in the relative volume or mass ratio between the left and the right ventricles.

7. Factors of decreased as well as increased excitability may be present.

8. These factors in part or all may operate together.

It is felt that some of these factors might give a more comprehensive idea of the influence of cardiodynamics on the activity of the heart.

CONCLUSIONS

1. Electrocardiographic evidence of right and left axis deviation was produced in the intact dog under ether anesthesia by distention of the respective ventricles.

2. Acute dilation of the right ventricle was produced in the intact dog with corresponding right axis deviation.

3. Possible factors for the production of axis deviation and various arrhythmias of the heart are suggested.

4. The possible importance of these and similarly acting factors as a mechanism for clinical changes of the electrocardiogram is discussed.

Book Reviews

BODILY CHANGES IN PAIN, HUNGER, FEAR AND RAGE. By WALTER B. CANNON. Second edition. Price, $3. New York: D. Appleton & Company, 1929.

In this second edition the author presents in the first eleven chapters an entirely logical sequence of the researches of many years on the autonomic system, the nervous control of the suprarenals and the sympathicomimetic function of "adrenin," including the external manifestations in the hair, pupils, etc., the increased blood sugar, the increased muscular blood flow, decreased peristalsis, increased cardiac action, restorative effects on muscular fatigue, increased coagulability of blood and increased number of red cells. In all of the conditions mentioned a close parallelism is shown between the changes occurring during pain, fear, rage and other violent emotions and the similar changes produced by "adrenin" therefore, proving, apparently, that "adrenin" is the producer of such changes normally during emotional excitement.

Beginning with the twelfth chapter the author distinguishes clearly between the facts as they are, and they do seem incontrovertible, and the interpretation of the data. To Cannon there is a definite utility of the body changes occurring in pain and great emotion. He is willing to admit, however, that this is a matter of opinion and offers to welcome a more reasonable theory when it appears. To psychologists the last few chapters on the energizing effects of emotional excitement and the denial of the evidence and interpretation on which the James-Lange theory of the emotions is based will furnish extremely stimulating reading. Hunger and thirst are discussed in an interesting fashion although here again there is room for difference of opinion. Cannon's theory of thirst reminds one somewhat of a much more elementary conception expressed by Francis Beaumont.

The intelligent layman and others who may believe in the eventual disappearance of war will find considerable pleasure in the last chapter, which deals with the substitution of international athletic competitions for the more destructive means of settling international disputes.

It is to be regretted that the book was published before the complete details on the sympathectomized animals produced by the author were available, as these animals show a definite ability to carry on the ordinary activities of a peaceful life but are completely inferior in respect to sudden readjustments required by the emergencies of life. The book is definitely a classic on the subject.

THE CLINICAL ASPECTS OF VENOUS PRESSURE. By J. A. E. EYSTER. Price, $2.50. New York: The Macmillan Company, 1929.

This book contains an excellent and clear discussion of the physiology of cardiac function and its relationship to arterial and venous pressure. The method of measuring venous pressure as devised by Hooker and Eyster and later modified by Eyster is given in full detail. The relationship of increased venous pressure to the various signs and symptoms of cardiac failure is adequately demonstrated, and it is pointed out that single readings mean little while the course of the venous pressure curve has much more significance. The author franky admits that the usefulness of venous pressure estimation is limited to the narrow field of cardiac failure since a high venous pressure is found in practically no other general conditions. There is, however, no definite evidence that in the ordinary ambulatory case with fairly good cardiac reserve, a venous pressure determination would tell one more as to prognosis in regard to eventual failure than the ordinary careful history and examination of the patient. It is erroneous to draw conclusions from the cutaneous capillary pressures to those existing in the glomeruli, as does the author.

The bibliography is complete except for failure to mention the changes occurring in the venous pressure in pregnancy. On the whole this small volume will prove useful to physiologists and clinicians interested in the subject.

THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR. VOLUME X. NEUROPSYCHIATRY. Price, $2.25. Washington, D. C.: United States Government Printing Office, 1929.

Attention is called in the preface to the unusual opportunity offered to study statistically a large number of neuropsychiatric disorders with a uniform method of recording. It gives one a fairly accurate estimate of the percentage of nervous and mental disability present in the male population liable for military service, and also the types of nervous disorders which develop as a result of war activity. Attention is called to the large number of persons who in civil life passed as practically normal and who were actually suffering from a severe psychoneurosis which rendered them unfit for military duty. By far the most frequent cause for discharge was dementia praecox, mental deficiency second and epilepsy third. None of this group developed as a result of the war. The most important functional neurosis was "shell shock." The author states that there is still a controversy as to whether the cause of shell shock was mainly physical or mental. All, however, agree that the constitutional make-up of the person was a decided contributing factor.

A great deal of time and thought has been expended in the preparation of this volume and the results are most pleasing.

NEPHRITIS: ITS PROBLEMS AND TREATMENT. By T. I. BENNETT. London: Oxford Medical Publications.

This volume contains a critical survey of nephritis and deals concisely with its clinical features and treatment. The author emphasizes the inadequacy of present forms of classification, but suggests that renal lesions of the type under discussion may occur as nephrosis, glomerulonephritis and arteriosclerosis with renal manifestations. He leans toward the conception that nephrosis is a part of a general metabolic disturbance in which the kidney shows only one phase. Infection is considered the most probable cause of glomerulonephritis. The author considers that arteriosclerosis with renal manifestations can best be explained by assuming that the arteriolar involvement antedates the renal changes, and that the nephritis is either a result of the vascular change, or due to the same cause which produces an abnormal condition of the arterioles.

Brief discussion of the more important symptoms is offered. The similarity between uremia and tetany is pointed out, particularly the low calcium content in the blood. Edema is considered as due to the causes of renal disease rather than to the nephritis.

Treatment for the various forms of renal disease is discussed, and lists of diets are appended.

TOBACCO AND PHYSICAL EFFICIENCY. By PIERRE SCHRUMPF-PIERRON, M.D., Professor of Clinical Medicine, University of Cairo. Published under the Auspices of the Committee to Study the Tobacco Problem. Cloth. Price, $1.85. Pp. 134. New York: Paul B. Hoeber, Inc., 1927.

This monograph is the "first really complete compendium of the vast amount of literature of various countries concerning the effects of tobacco on the human system." As is the case with alcohol, the study of the effects of the use of tobacco is still incomplete. It has been difficult to obtain scientifically precise knowledge of the effect of tobacco on its users because of great variations in individual susceptibility, the forms of use as well as difference in grades and quality used and particularly the lack of data available as to the influence of tobacco as ordinarily used among large groups of people as compared with a similar group of abstainers. Well controlled clinical and laboratory studies are needed.

Therefore, no conclusions are drawn. Each chapter presents a fair, sane exposition of existing knowledge and opinion. An extensive bibliography of seventy-six pages is appended.

PRINCIPLES OF MEDICAL TREATMENT. By GEORGE CHEEVER SHATTUCK, M.D., A.M., Harvard Medical School. Sixth edition, revised and enlarged. Cloth. Price, $3.50. Pp. 256. Cambridge, Mass.: Harvard University Press, 1927.

This edition has been greatly enlarged, both by the revision and expansion of material given in the earlier editions and by the addition of several new chapters on asthma, syphilis, lead poisoning, anemia, endocrine disorders, preoperative and postoperative medical treatment and vaccine therapy.

The principles of treatment are briefly elucidated and are based largely on accepted scientific knowledge. Many useful tables and diets are included and the chapter on medication deserves particular commendation, in that it is devoted to the intelligent use of relatively few drugs, vaccines, gland extracts, serums, etc.

The book should prove particularly valuable to the practitioner when time is available for quick reference only.

ORIGIN OF MALIGNANT TUMORS. By THEODOR BOVERI. Translated by Marcella Boveri. Price, $2.50. Baltimore: Williams & Wilkins Company, 1929.

Another theory for the development of malignant tumors is added to the long list. The author's work on mitoses in eggs of sea urchins serves as the basis for his belief that tumors arise from a single primordial cell, and that their characteristics as neoplastic cells are due to a "wrongly combined chromosome complex." This abnormality in distribution of chromosomes is the result of multipolar mitosis brought about by a variety of conditions. Little is said concerning what these conditions are. Admitting the author's theory we are thus still without knowing the cause of malignant tumors; the theory propounded being, in the last analysis, concerned only with the mechanism of neoplastic development once this has begun.

The volume is primarily of interest to the cytophysiologist. The style makes it difficult reading for others. This treatise, however, should serve to stimulate further interest in the study of the individual neoplastic cells. Many questions for investigation along these lines are suggested.

THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR. VOLUME XII. PATHOLOGY OF THE ACUTE RESPIRATORY DISEASES AND OF GAS GANGRENE. Price, $3.60. Washington, D. C.: United States Government Printing Office, 1929.

The first 405 pages are given over to the discussion of respiratory infections, the remaining 170 pages to gas gangrene.

The pathology is discussed in detail, and this volume will serve as an accurate source of information for future generations. The volume is profusely illustrated with both black and white and colored plates of gross and microscopic specimens.

CORRECTION

The date of submission of the article by Dr. Benjamin I. Ashe, entitled, "The Hemoglobin Percentage and the Red Blood Cell Count in Bright's Disease, Myocardial Insufficiency and Hypertension," was incorrectly given in the October issue (**44**:506, 1929). It should read February, 1929, instead of June 18, 1929.

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